63 U.S.P.Q.2D 1609
296 F.3d 1316
**(Cite as: 63 U.S.P.Q.2d 1609)**



Enzo Biochem Inc.
v.
Gen-Probe Inc.

U.S. Court of Appeals Federal Circuit

No. 01-1230

Decided July 15, 2002

United States Patents Quarterly Headnotes

**PATENTS**
**[1] Patentability/Validity -- Specification -- Written description (§ 115.1103)**
Functional description of genetic material may be sufficient to satisfy written description requirement of 35 U.S.C. § 112, since requirement can be met by showing that invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, including functional characteristics when coupled with known or disclosed correlation between function and structure.
**[2] Patentability/Validity -- Specification -- Written description (§ 115.1103)**
Reference in specification to deposit of biological material in public depository, which makes its contents accessible to public when it is not otherwise available in written form, constitutes adequate description of deposited material sufficient to comply with the written description requirement of 35 U.S.C. § 112; in present case, in which patent in suit is directed to nucleic acid probes, reference in specification to deposits of nucleotide sequences describe those sequences sufficiently to public for purposes of meeting written description requirement.
**[3] Patentability/Validity -- Specification -- Written description (§ 115.1103)**
Written description requirement for generic claims is not necessarily met as matter of law merely because claim language is repeated verbatim in specification, since, even if claim is supported by specification, language of specification must, to extent possible, describe claimed invention so that one skilled in art can recognize what is claimed, and appearance of mere indistinct words in specification or claim does not satisfy that requirement; specification does not necessarily describe invention by indicating that applicant "possessed" invention as of desired filing date, since ensuring that applicant had possession of invention is one purpose of description requirement, but possession alone is not always sufficient to satisfy that requirement.
**[4] Patentability/Validity -- Date of invention -- Reduction to practice (§ 115.0405)**
**Patentability/Validity -- Specification -- Written description (§ 115.1103)**
Proof of reduction to practice, absent adequate description in specification of what is reduced to practice, does not satisfy written description requirement of 35 U.S.C. § 112, since proof of reduction to practice may show priority of invention, but it does not by itself provide written description in patent's specification; in present case, patentee's disclosure of actual reduction to practice is not "safe haven" by which it has demonstrated compliance with description requirement.

**PATENTS**
**Particular patents -- Chemical -- Nucleic acid probes**
4,900,659, Lo and Yang, nucleotide sequence composition and method for detection of Neisseria gonorrhoeae and method for screening for a nucleotide sequence that is specific for a genetically distinct group, summary judgment of invalidity reversed on rehearing.

***1609** Appeal from the U.S. District Court for the Southern District of New York, Hellerstein, J.

Action by Enzo Biochem Inc. against Gen-Probe Inc., Chugai Pharma U.S.A. Inc., Chugai Pharmaceutical Co. Ltd., Biomerieux Inc., Becton Dickinson and Co., and Biomerieux SA for patent infringement. Summary judgment of patent invalidity was affirmed on appeal in panel opinion issued April 2, 2002 ( 62 USPQ2d 1289). On plaintiff-appellant's petition for rehearing, case was referred to merits panel that heard appeal. Petition granted; prior decision vacated; district court's grant of summary judgment reversed and remanded.

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Mark S. Davies, attorney, Robert D. McCallum Jr., assistant attorney general, and Scott R. McIntosh, attorney, U.S. Department of Justice, Washington, for amicus curiae United States in support of rehearing en banc.

Before Lourie, Dyk, and Prost, circuit judges.

Lourie, J.

ON PETITION FOR REHEARING

Enzo Biochem, Inc. petitions for rehearing of this appeal following our prior decision, reported at 285 F.3d 1013, 62 USPQ2d 1289 (Fed. Cir. 2002), in which we affirmed the decision of the United States District Court for the Southern District of New York. The district court had granted Gen-Probe Incorporated, Chugai Pharma U.S.A., Inc., Chugai Pharmaceutical Co., Ltd., Biomerieux, Inc., Biomerieux SA, and Becton Dickinson and Company's (collectively, "the defendants'") motion for summary judgment that claims 1-6 of U.S. Patent 4,900,659 are invalid for failure to meet the written description requirement of 35 U.S.C. § 112, ¶ 1. *Enzo Biochem, Inc. v. Gen-Probe Inc.*, No. 99 Civ. 4548 (S.D.N.Y. Apr. 4, 2001) (final order). Having considered Enzo's petition for rehearing and the defendants' response, [FN1] we have determined that our prior decision that a deposit may not satisfy the written description requirement was incorrect. We therefore grant Enzo's petition for rehearing, vacate the prior decision, and reverse the district court's grant of summary judgment that Enzo's claims are invalid for failure to meet the written description requirement. Because genuine issues of material fact exist regarding satisfaction of the written description requirement, we remand.

BACKGROUND

Enzo is the assignee of the '659 patent, which is directed to nucleic acid probes that selectively hybridize to the genetic material of the bacteria that cause gonorrhea, *Neisseria gonorrhoeae*. *N. gonorrhoeae* reportedly has between eighty and ninety-three percent homology with *Neisseria meningitidis*. '659 patent, col. 2, ll. 61-64. Such a high degree of homology has made detection of *N. gonorrhoeae* difficult, as any probe capable of detecting *N. gonorrhoeae* may also show a positive result when only *N. meningitidis* is present. Enzo recognized the need for a chromosomal DNA probe specific for *N. gonorrhoeae*, and it derived three such sequences that preferentially hybridized to six common strains of *N. gonorrhoeae* over six common strains of *N. meningitidis*. *Id.* at col. 3, l. 49 to col. 4, l. 14; col. 4, ll. 45-50. The inventors believed that if the preferential hybridization ratio of *N. gonorrhoeae* to *N. meningitidis* were greater than about five to one, then the "discrete nucleotide sequence [would] hybridize to virtually all strains of *Neisseria gonorrhoeae* and to no strain of *Neisseria meningitidis*." *Id.* at col. 12, ll. 60-65. The three sequences that the inventors actually derived had a selective hybridization ratio of greater than fifty. *Id.* at col. 13, ll. 9-15. Enzo deposited those sequences in the form of a recombinant DNA molecule within an *E. coli* bacterial host at the American Type

Culture Collection. *Id.* at col. 13, ll. 27-31.

Claim 1 is as follows:

1.A composition of matter that is specific for *Neisseria gonorrhoeae* comprising at least one nucleotide sequence *for which the ratio of the amount of said sequence which hybridizes to chromosomal DNA of Neisseria gonorrhoeae to the amount of said sequence which hybridizes to chromosomal DNA of Neisseria meningitidis is greater than about five*, said ratio being obtained by a method comprising the following steps;

(a) providing a radioactively labeled form of said nucleotide sequence;

***1611** (b) providing a serial dilution series of purified chromosomal DNA from each of the *N. gonorrhoeae* strains; (1) ATCC 53420, (2) ATCC 53421, (3) ATCC 53422, (4) ATCC 53423, (5) ATCC 53424, (6) ATCC 53425, and forming test dots from each of said dilution series on a matrix;

(c) providing a serial dilution series of purified nucleotide sequences from each of the *N. meningitidis* strains: (1) ATCC 53414, (2) ATCC 53415, (3) ATCC 53416, (4) ATCC 53417, (5) ATCC 53418, (6) ATCC 53419, and forming test dots from each of said dilution series on a matrix;

(d) hybridizing equal portions of the labeled nucleotide sequences to the matrix provided in step (b) and (c), respectively; wherein the hybridization is conducted in a solution having a salt concentration of 2X SSC at (i) 65° C. in cases in which the sequence has greater than 50 base pairs or (ii) at Tm (° C.) minus 30° C. in cases in which the sequence has less than 50 base pairs, wherein Tm is the denaturation temperature of the sequence;

(e) quantifying the labeled nucleotide sequence hybridized in step (d) to each test dot;

(f) subtracting from the data of step (e) an averaged amount of radioactivity attributable to background to obtain a corrected amount of hybridized radioactivity at each test dot;

(g) normalizing the data of step (f) by multiplying the amount of corrected radioactivity at each test dot by a factor which adjusts the amount of radioactivity to equal amounts of chromosomal DNA at each test dot;

(h) selecting two normalized values that are most nearly the same and that correspond to adjacent members of the dilution series for each of the above strains of *N. gonorrhoeae* and obtaining the average of the selected values;

(i) selecting two normalized values that are most nearly the same and that correspond to adjacent members of the dilution series for each of the above strains of *N. meningitidis* and obtaining the average of the selected values;

(j) dividing the lowest average obtained in step (h) by the highest average obtained in step (i) to obtain said ratio. *Id.* at col. 27, l. 29 to col. 28, l. 27 (emphasis added). Claims 2 and 3 depend from claim 1 and further limit the hybridization ratio to greater than about twenty-five and fifty, respectively. *Id.* at col. 2, ll. 27-30. Claim 4 is directed to the three deposited sequences (referenced by their accession numbers) and variants thereof as follows:

4. The composition of claim 1 wherein said nucleotide sequences are selected from the group consisting of:

a. the *Neisseria gonorroheae* [sic] DNA insert of ATCC 53409, ATCC 53410 and ATCC 53411, and discrete nucleotide subsequences thereof,

b. mutated discrete nucleotide sequences of any of the foregoing inserts that are within said hybridization ratio and subsequences thereof; and

c. mixtures thereof. *Id.* at col. 28, ll. 31-39. Claim 5 is directed to an assay for detection of *N. gonorrhoeae* using the composition of claim 1. *Id.* at ll. 40-46. Claim 6 further limits the method of claim 5 to the nucleotide sequences that Enzo deposited ( *i.e.*, those in claim 4) and variants thereof. *Id.* at ll. 47-56.

Enzo sued the defendants for infringement of the '659 patent, and the defendants moved for summary judgment that the claims were invalid for failure to meet the written description requirement of 35 U.S.C. § 112, ¶ 1. The district court, in oral remarks from the bench, granted that motion. Tr. of

Hr'g at 42, *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, No. 99-CV-4548 (S.D.N.Y. Jan. 24, 2001). It concluded that the claimed composition of matter was defined only by its biological activity or function, *viz.*, the ability to hybridize to *N. gonorrhoeae* in a ratio of better than about five with respect to *N. meningitidis*, which it was held was insufficient to satisfy the § 112, ¶ 1 requirement set forth in this court's holdings in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), *Fiers v. Revel*, 984 F.2d 1164, 25 USPQ2d 1601 (Fed. Cir. 1993), and *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991). Tr. of Hr'g at 28. The court rejected ***1612** Enzo's argument that the reference in the specification to the deposits of biological materials in a public depository inherently disclosed that the inventors were in possession of the claimed sequences. *Id.* at 35. It distinguished this court's precedents concerning deposits as relating to the enablement requirement of § 112, ¶ 1. *Id.* at 38-40. Enzo appealed to this court; we have jurisdiction pursuant to 28 U.S.C. § 1295 (a)(1).

## DISCUSSION

Summary judgment is appropriate when there is no genuine issue of material fact and the moving party is entitled to judgment as a matter of law. Fed. R. Civ. P. 56(c); *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 247-48 (1986). On motion for summary judgment, the court views the evidence and any disputed factual issues in the light most favorable to the party opposing the motion. *Matsushita Elec. Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 587 (1986). A patent is presumed to be valid, 35 U.S.C. § 282 (1994), and this presumption can be overcome only by facts supported by clear and convincing evidence to the contrary, *see, e.g., WMS Gaming, Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1355, 51 USPQ2d 1385, 1396-97 (Fed. Cir. 1999). Compliance with the written description requirement is a question of fact. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991).

Enzo argues that the testimony of its expert, Dr. Wetmer, raised a genuine factual issue whether the reference to the deposits inherently described the claimed nucleotide sequences. Enzo also argues that its description of the binding affinity of the claimed nucleotide sequences satisfies the requirement set forth in the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, 66 Fed. Reg. 1099 (Jan. 5, 2001) (" *Guidelines*"). Enzo asserts that the court erred in not evaluating the patentability of the claims separately, pointing out that claims 4 and 6 are directed to the three deposited sequences and variations and mixtures thereof. Enzo further asserts that the claims *per se* meet the written description requirement because they appear *in ipsis verbis* in the written description. Enzo also argues that this court's articulation of the written description requirement for genetic material in *Eli Lilly* should not apply to this case because Enzo reduced the invention to practice and deposited the derived biological materials, thereby demonstrating its "possession" of the invention.

The defendants respond that the district court properly granted summary judgment because the patent described the claimed nucleotide sequences only by their function, which they state is insufficient to meet the requirements of § 112, ¶ 1 as a matter of law, even as to the narrower claims directed to the deposited materials. The defendants also assert that Dr. Wetmur's opinion that the deposited genetic materials could have been sequenced did not cure the actual failure of the inventors to identify them by some distinguishing characteristic, such as their structure. Moreover, the defendants point out that claims 4 and 6, which are directed to the deposited materials, each cover a broad genus of nucleic acids. The defendants also urge that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement. Finally, the defendants assert that the district court did not err in its determination that Enzo's "possession" of three nucleotide sequences that it reduced to practice and deposited nevertheless did not satisfy the written description requirement of § 112, ¶ 1.

The written description requirement of § 112, ¶ 1 is set forth as follows:

*The specification shall contain a written description of the invention*, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains or with which it

is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

35 U.S.C. § 112, ¶ 1 (1994) (emphasis added). We have interpreted that section as requiring a "written description" of an invention separate from enablement. *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1117 (recognizing the severability of the "written description" and "enablement" provisions of § 112, ¶ 1). Compliance with the written description requirement is essentially a fact-based inquiry that will "necessarily vary depending on the nature of the invention claimed." *Id.* (citing *In re DiLeone*, 436 F.2d 1404, 1405, 168 USPQ 592, 593 (CCPA 1971)). We have also previously considered the written description requirement ***1613** as applied to certain biotechnology patents, in which a gene material has been defined only by a statement of function or result, and have held that such a statement alone did not adequately describe the claimed invention. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. In *Eli Lilly*, we concluded that a claim to a micro-organism containing a human insulin cDNA was not adequately described by a statement that the invention included human insulin cDNA. *Id.* at 1567, 43 USPQ2d at 1405. The recitation of the term human insulin cDNA conveyed no distinguishing information about the identity of the claimed DNA sequence, such as its relevant structural or physical characteristics. *Id.* We stated that an adequate written description of genetic material "'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention," and that none of those descriptions appeared in that patent. *Id.* at 1566, 43 USPQ2d at 1404 (quoting *Fiers*, 984 F.2d at 1171, 25 USPQ2d at 1606). The specification in the *Eli Lilly* case thus did not show that the inventors had possession of human insulin cDNA.

[1] It is not correct, however, that all functional descriptions of genetic material fail to meet the written description requirement. The PTO has issued Guidelines governing its internal practice for addressing that issue. The Guidelines, like the Manual of Patent Examining Procedure ("MPEP"), are not binding on this court, but may be given judicial notice to the extent they do not conflict with the statute. *See Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1180 n.10, 33 USPQ2d 1823, 1828 n.10 (Fed. Cir. 1995). In its Guidelines, the PTO has determined that the written description requirement can be met by "show [ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics." *Guidelines*, 66 Fed. Reg. at 1106 (emphasis added). For example, the PTO would find compliance with § 112, ¶ 1, for a claim to an "isolated antibody capable of binding to antigen X," notwithstanding the functional definition of the antibody, in light of "the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature." Synopsis of Application of Written Description Guidelines, at 60, *available at* http://www.uspto.gov/web/patents/guides.htm ("*Application of Guidelines*"). Thus, under the Guidelines, the written description requirement would be met for all of the claims of the '659 patent if the functional characteristic of preferential binding to *N. gonorrhoeae* over *N. meningitidis* were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed. We are persuaded by the Guidelines on this point and adopt the PTO's applicable standard for determining compliance with the written description requirement.

Applying those principles, we first inquire whether Enzo's deposits of the claimed nucleotide sequences of claims 4 and 6 may constitute an adequate description of those sequences. Secondly, we will consider whether the description requirement is met for all of the claims on the basis of the functional ability of the claimed nucleotide sequences to hybridize to strains of *N. gonorrhoeae* that are accessible by deposit.

[2] As to the first question, Enzo asserts that the claimed sequences are inherently described by reference to deposits of three sequences that are within the scope of its claims. Whether reference to a deposit of a nucleotide sequence may

adequately describe that sequence is an issue of first impression in this court. In light of the history of biological deposits for patent purposes, the goals of the patent law, and the practical difficulties of describing unique biological materials in a written description, we hold that reference in the specification to a deposit in a public depository, which makes its contents accessible to the public when it is not otherwise available in written form, constitutes an adequate description of the deposited material sufficient to comply with the written description requirement of § 112, ¶ 1.

The practice of depositing biological material arose primarily to satisfy the enablement requirement of § 112, ¶ 1. For example, in *In re Argoudelis*, the patent application claimed antibiotic compounds that were produced by a microorganism. 434 F.2d 1390, 1390, 168 USPQ 99, 100 (CCPA 1970). The applicants deposited the microorganism because they ***1614** could not "sufficiently disclose by written word how to obtain the microorganism starting material from nature." *Id.* at 1392, 168 USPQ at 102. By making the biological material accessible to the public, they enabled the public to make and use the claimed antibiotics. *Id.* at 1393, 168 USPQ at 102-03. In *Amgen*, we noted the relevance of deposit practice to satisfaction of the enablement requirement but rejected the defendants' argument that a deposit was necessary in that case to satisfy the best mode requirement of § 112, ¶ 1. *See* 927 F.2d at 1210, 18 USPQ2d at 1024; *see also In re Lundak*, 773 F.2d 1216, 1217, 227 USPQ 90, 92 (Fed. Cir. 1985) (discussing deposit practice primarily in relation to an enablement rejection and noting that "[a]n accession number and deposit date add nothing to the written description of the invention" in the context of proven availability of a cell line prior to filing date).

Recognizing the importance of biological deposits to patent practice, the PTO has promulgated rules to address the procedural requirements relating to such deposits, but it has declined to expressly correlate substantive requirements relating to deposits with particular statutory requirements. *See* Deposit of Biological Materials for Patent Purposes, 53 Fed. Reg. 39,420, 39,425 (Oct. 6, 1988) (notice of proposed rules) (codified at 37 C.F.R. Part 1) ("The rules are not intended to address which requirements of 35 U.S.C. 112 may be met by the making of deposits."). The Office does offer guidance, however, in determining when a deposit may be necessary, such as "[w]here the invention involves a biological material and words alone cannot sufficiently describe how to make and use the invention in a reproducible manner." MPEP § 2402 (8th ed. Aug. 2001). The PTO has also issued a regulation stating when a deposit is not necessary, *i.e.*, "if it is known and readily available to the public or can be made or isolated without undue experimentation." 37 C.F.R. § 1.802(b) (2001). Inventions that cannot reasonably be enabled by a description in written form in the specification, but that otherwise meet the requirements for patent protection, may be described in surrogate form by a deposit that is incorporated by reference into the specification. While deposit in a public depository most often has pertained to satisfaction of the enablement requirement, we have concluded that reference in the specification to a deposit may also satisfy the written description requirement with respect to a claimed material.

In this case, Enzo's deposits were incorporated by reference in the specification. A person of skill in the art, reading the accession numbers in the patent specification, can obtain the claimed sequences from the ATCC depository by following the appropriate techniques to excise the nucleotide sequences from the deposited organisms containing those sequences. '659 patent, col. 13, ll. 27-36. The sequences are thus accessible from the disclosure in the specification. Although the structures of those sequences, *i.e.*, the exact nucleotide base pairs, are not expressly set forth in the specification, those structures may not have been reasonably obtainable and in any event were not known to Enzo when it filed its application in 1986. *See* '659 patent, col. 3, ll. 40-46 (noting severe time constraints in sequencing DNA). We therefore agree with Enzo that reference in the specification to deposits of nucleotide sequences describe those sequences sufficiently to the public for purposes of meeting the written description requirement.

As the defendants point out, however, Enzo's claims 4 and 6 are not limited to the deposited sequences. Claim 4 is directed to nucleotide sequences that are selected from the group consisting of the three deposited sequences, "discrete nucleotide subsequences thereof . . .

mutated discrete nucleotide sequences of any of the foregoing inserts that are within said hybridization ratio and subsequences thereof[,] and . . . mixtures thereof." '659 patent, col. 28, ll. 31-39. Claim 6 is also similarly directed to the three deposited sequences and subsequences and mutated variations thereof. *Id.* at ll. 47-56. The specification defines a subsequence non-specifically as a nucleotide sequence "greater than about 12 nucleotides." '659 patent, col. 3, ll. 29- 30. As the deposited sequences are about 850, 850, and 1300 nucleotides long, *id.* at col. 13, ll. 47-49, there are at least hundreds of subsequences of the deposited sequences, an unknown number of which might also meet the claimed hybridization ratio. Moreover, Enzo's expert, Dr. Wetmur, stated that "astronomical" numbers of mutated variations of the deposited sequences also fall within the scope of those claims, and that such broad claim scope is necessary to adequately protect Enzo's invention from copyists who could otherwise ***1615** make a minor change to the sequence and thereby avoid infringement while still exploiting the benefits of Enzo's invention. The defendants assert that such breadth is fatal to the adequacy of the written description. On the other hand, because the deposited sequences are described by virtue of a reference to their having been deposited, it may well be that various subsequences, mutations, and mixtures of those sequences are also described to one of skill in the art. We regard that question as an issue of fact that is best resolved on remand. [FN2] Because the district court's grant of summary judgment was based on its conclusion that Enzo's deposits could not satisfy the written description requirement as a matter of law, we reverse the district court's grant of summary judgment that claims 4 and 6 are invalid for failure to meet the written description requirement. On remand, the court should determine whether a person of skill in the art would glean from the written description, including information obtainable from the deposits of the claimed sequences, subsequences, mutated variants, and mixtures sufficient to demonstrate possession of the generic scope of the claims.

We next address the question whether the compositions of the broader genus claims 1-3 and 5 are sufficiently described to meet the requirements of § 112, ¶ 1, on the basis of Enzo's deposits of three sequences. If those sequences are representative of the scope of the genus claims, *i.e.*, if they indicate that the patentee has invented species sufficient to constitute the genera, they may be representative of the scope of those claims. *See In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) (discussing circumstances in which a species may be representative of and therefore descriptive of genus claims). Because the district court concluded that the deposited sequences were not themselves described, it did not determine whether that description was representative of the genera in those claims. Such determination should be made on remand.

When we addressed a similar issue in *Eli Lilly*, we determined that a disclosure of the sequence of rat cDNA was not descriptive of the broader invention consisting of mammalian and vertebrate cDNA, although it was a species falling within the scope of those claims. *Eli Lilly*, 119 F.3d at 1567-68, 43 USPQ2d at 1405. In *Eli Lilly*, the specification and generic claims to all cDNAs encoding for vertebrate or mammalian insulin did not describe the claimed genus because they did not set forth any common features possessed by members of the genus that distinguished them from others. *Id.* at 1568, 43 USPQ2d at 1405. Nor did the specification describe a sufficient number of species within the very broad genus to indicate that the inventors had made a generic invention, *i.e.*, that they had possession of the breadth of the genus, as opposed to merely one or two such species. *Id.* The PTO has included a hypothetical example based on the facts of *Eli Lilly* in its Synopsis of Application of Written Description Guidelines in which the description requirement is not met. *See Application of Guidelines*, Example 17, at 61-64. The PTO has also provided a contrasting example of genus claims to nucleic acids based on their hybridization properties, and has determined that such claims may be adequately described if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar. *See id.*, Example 9, at 35-37. Whether the disclosure provided by the three deposits in this case, coupled with the skill of the art, describes the genera of claims 1-3 and 5 is a fact question the district court did not address. On remand, the district court should determine, consistently with the precedent of this court and the PTO's Guidelines, whether one skilled in the art would consider the subject matter of claims 1-3 and 5 to be adequately described,

recognizing the significance of the deposits and the scope of the claims.

Enzo argues that all of the claims are adequately described on another basis, *viz.*, by means of the disclosed correlation of the function of hybridization with the bacterial DNA. In its petition for rehearing, Enzo states as attorney argument that "[t]he description and claiming of biological materials by their affinity to other materials that are clearly identified in the specification and claims (the particular deposited strains of *N. gonorrhoeae* and *N. meningitidis*) inherently specifies structure, and is routine in this field." Claim 1 sets forth ***1616** the deposit numbers of six strains of *N. gonorrhoeae* to which the claimed nucleotide sequences preferentially hybridize, as well as the deposit numbers of six strains of *N. meningitidis* that are thereby distinguished. Again, as with the claimed nucleotide sequences, the sequences of the genomic DNA of those bacteria are not disclosed, perhaps because such sequencing would have been unduly burdensome at the time of Enzo's invention. '659 patent, col. 3, ll. 40-46 (noting that it would take 3,000 scientists one month to sequence the genome of one strain of *N. gonorrhoeae* and one strain of *N. meningitidis*). However, as those bacteria were deposited, their bacterial genome is accessible and, under our holding today, they are adequately described in the specification by their accession numbers. Because the claimed nucleotide sequences preferentially bind to the genomic DNA of the deposited strains of *N. gonorrhoeae* and have a complementary structural relationship with that DNA, those sequences, under the PTO Guidelines, may also be adequately described. Although the patent specification lacks description of the location along the bacterial DNA to which the claimed sequences bind, Enzo has at least raised a genuine issue of material fact as to whether a reasonable fact-finder could conclude that the claimed sequences are described by their ability to hybridize to structures that, while not explicitly sequenced, are accessible to the public. Such hybridization to disclosed organisms may meet the PTO's Guidelines stating that functional claiming is permissible when the claimed material hybridizes to a disclosed substrate. That is a fact question. We therefore conclude that the district court erred in granting summary judgment that the claims are invalid for failure to meet the written description requirement. On remand, the court should consider whether one of skill in the art would find the generically claimed sequences described on the basis of Enzo's disclosure of the hybridization function and an accessible structure, consistent with the PTO Guidelines. If so, the written description requirement would be met.

> [3] We next address Enzo's additional argument that the written description requirement for the generic claims is necessarily met as a matter of law because the claim language appears *in ipsis verbis* in the specification. We do not agree. Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. One may consider examples from the chemical arts. A description of an anti-inflammatory steroid, *i.e.*, a steroid (a generic structural term) described even in terms of its function of lessening inflammation of tissues fails to distinguish any steroid from others having the same activity or function. Similarly, the expression "an antibiotic penicillin" fails to distinguish a particular penicillin molecule from others possessing the same activity. A description of what a material does, rather than of what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Id.*

In *Eli Lilly*, we were faced with a set of facts in which the words of the claim alone did not convey an adequate description of the invention. *Id.* at 1567, 43 USPQ2d at 1405. In such a situation, regardless whether the claim appears in the original specification and is thus supported by the specification as of the filing date, § 112, ¶ 1 is not necessarily met. *See Guidelines* at 1100 (noting *Eli Lilly*'s clarification of the "original claim" doctrine in situations in which the name of the claimed material does not convey sufficient identifying information). If a purported description of an invention does not meet the requirements of the statute, the fact that it appears as an original claim or in the specification does not save it. A claim does not become more descriptive by its repetition, or its

longevity.

Inasmuch as § 112, ¶ 1 requires such description, we are not persuaded by Enzo's argument that, because the specification indicated that Enzo "possessed" the claimed invention by reducing three sequences within the scope of the claims to practice, Enzo necessarily described the invention. It is true that in *Vas-Cath*, we stated: "The purpose of the 'written description' requirement is broader than to merely explain how to 'make and use'; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." ***1617** *Vas-Cath*, 935 F.2d at 1563-64, 19 USPQ2d at 1117. That portion of the opinion in *Vas-Cath*, however, merely states a *purpose* of the written description requirement, *viz.*, to ensure that the applicant had possession of the invention as of the desired filing date. It does not state that possession alone is always sufficient to meet that requirement. Furthermore, in *Lockwood v. American Airlines, Inc.*, we rejected Lockwood's argument that "all that is necessary to satisfy the description requirement is to show that one is 'in possession' of the invention." 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Rather, we clarified that the written description requirement is satisfied by the patentee's disclosure of "such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention." *Id.*

The articulation of the written description requirement in terms of "possession" is especially meaningful when a patentee is claiming entitlement to an earlier filing date under 35 U.S.C. §§ 119 or 120, in interferences in which the issue is whether a count is supported by the specification of one or more of the parties, and in *ex parte* applications in which a claim at issue was filed subsequent to the application. *See Vas-Cath*, 935 F.2d at 1560, 19 USPQ2d at 1114 (describing situations in which the written description requirement may arise); *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (noting, in the context of claiming entitlement to the priority date of an earlier application, that the written description requirement is met if "the disclosure of the application relied upon reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter"). Application of the written description requirement, however, is not subsumed by the "possession" inquiry. A showing of "possession" is ancillary to the *statutory* mandate that "[t]he specification shall contain a written description of the invention," and that requirement is not met if, despite a showing of possession, the specification does not adequately describe the claimed invention. After all, as indicated above, one can show possession of an invention by means of an affidavit or declaration during prosecution, as one does in an interference or when one files an affidavit under 37 C.F.R. § 1.131 to antedate a reference. However, such a showing of possession alone does not cure the lack of a written description in the specification, as required by statute.

[4] Similarly, we conclude that proof of a reduction to practice, absent an adequate description in the specification of what is reduced to practice, does not serve to describe or identify the invention for purposes of § 112, ¶ 1. As with "possession," proof of a reduction to practice may show priority of invention or allow one to antedate a reference, but it does not by itself provide a written description *in the patent specification*. We are thus not persuaded by Enzo's argument, relying on the PTO's Guidelines, that its disclosure of an actual reduction to practice is an important "safe haven" by which it has demonstrated compliance with the description requirement. The Guidelines state:

Actual reduction to practice may be crucial in the relatively rare instances where the level of knowledge and level of skill are such that those of skill in the art cannot describe a composition structurally, or specify a process of making a composition by naming components and combining steps, in such a way as to distinguish the composition with particularity from all others. *Guidelines*, 66 Fed. Reg. at 1101. For biological inventions, for which providing a description in written form is not practicable, one may nevertheless comply with the written description requirement by publicly depositing the biological material, as we have held today. That compliance is grounded on the fact of the deposit and the accession number in the specification, not because a reduction to practice has occurred. Such description is the *quid pro quo* of the patent system; the public must receive meaningful disclosure in exchange for being excluded from practicing the invention for a

limited period of time.

CONCLUSION

For the foregoing reasons, we conclude that the district court erred in granting summary judgment that the claims of the '659 patent are invalid for failure to meet the written description requirement of § 112, ¶ 1. While the district judge clearly understood and correctly applied this court's existing precedent, we nevertheless reverse because this case has taken us into new territory and we have held, as a matter of first impression, that reference ***1618** in a patent specification to a deposit of genetic material may suffice to describe that material. We therefore remand for further resolution consistent with this opinion.

REVERSED and REMANDED

FN1. *Amicus curiae* briefs were filed by the United States Patent and Trademark Office and Fish & Richardson P.C.

FN2. We do not address the issue whether the breadth of the claim may implicate other validity issues, such as enablement. Only written description is before us.

C.A.Fed.

63 U.S.P.Q.2D 1609

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39 U.S.P.Q.2d 1225
1995 WL 735547 (S.D.Ind.)
**(Cite as: 39 U.S.P.Q.2d 1225)**



University of California
v.
Eli Lilly and Co.

U.S. District Court Southern District of Indiana

MDL Docket No. 912 No. IP-92-0224-C-D/G

Decided December 11, 1995

United States Patents Quarterly Headnotes

PATENTS
**[1] Infringement -- Doctrine of equivalents -- In general (Section 120.0701)**
Accused plasmid containing semisynthetic human proinsulin DNA sequence does not infringe, under doctrine of equivalents, claims of patent for recombinant bacterial plasmids containing coding sequences of insulin genes, since proinsulin encoding sequence of accused plasmid is "tailored" to begin precisely at first amino acid for human proinsulin, since patent in suit, properly interpreted, fails to provide tailoring techniques necessary to enable one skilled in art to prepare such coding sequence, since claims therefore cannot be read to encompass plasmids and microorganisms containing tailored coding sequences, and since plasmid made by method of patent in suit would not perform in substantially same way nor result in same product as would plasmid containing tailored coding sequence used by defendant.

PATENTS
**[2] Patent construction -- Claims -- Broad or narrow (Section 125.1303)**
Language of claim for specific semisynthetic sequence coding for human proinsulin, in which amino acid at position one of sequence is preceded by codon for methionine, does not demonstrate examiner's willingness to allow plaintiff to claim fusion protein expression of proinsulin, as well as direct expression, in patent in suit, since credible expert testimony shows that methionine is "start" codon that signals cell to begin producing protein from DNA sequence, that no substance can be expressed via technology in issue without start codon, and that direct expression takes place through use of start codon.

PATENTS
**[3] Infringement -- Construction of claims (Section 120.03)**
**Infringement -- Literal infringement (Section 120.05)**
Claims for DNA transfer vector and microorganism containing human proinsulin genes are not literally infringed by accused plasmid that employs fusion protein, since prosecution history of patent in suit indicates that DNA transfer vectors containing human proinsulin fusion proteins were in prior art, that examiner found asserted claims to be patentable only to extent that they claimed coding for direct expression of human proinsulin, and that fusion proteins are therefore excluded from scope of claims.

PATENTS
**[4] Infringement -- Doctrine of equivalents -- In general (Section 120.0701)**
Determination of infringement by equivalence, even if facts of case are considered under function-way-result test alone, requires more than consideration of result, and consideration of evidence of function-way-result may not be sufficient in every case, since court must consider all evidence relevant to substantiality of differences between accused and patented products; in present case, accused plasmid containing semisynthetic human proinsulin DNA sequence does not infringe, under doctrine of equivalents, claims for transfer vector containing human proinsulin genes, since claimed transfer vector only encompasses sequence of bases coding for proinsulin found in human source, and since accused plasmid employs fusion protein concept and does not consist of cDNA for human proinsulin.

PATENTS
**[5] Patentability/Validity -- Specification -- Written description (Section 115.1103)**
Patent specification that only describes cDNA for rat insulin does not provide adequate written description for insulin cDNA of vertebrate and

mammal genera, or for that of human species in particular, since inventors did not isolate and characterize human insulin cDNA until almost two years after patent application was filed, and therefore were not in possession of that DNA at time of application, since adequate written description of DNA requires "precise definition," and since isolation and characterization of proinsulin cDNA from one member of genus is not sufficient to support claims to insulin cDNA of thousands of other species from that genus.

PATENTS
**[6] Patentability/Validity -- Anticipation -- Identity of elements (Section 115.0704)**
**Patentability/Validity -- Obviousness -- Person of ordinary skill in art (Section 115.0902)**
Fact that those skilled in art, practicing invention of prior patent, would have been required to refer to second source in order to ascertain DNA sequence for human proinsulin does not alone preclude finding that prior patent anticipates asserted claims for transfer vector and microorganism containing human proinsulin genes, since extrinsic evidence is admissible to explain disclosure of reference in situations in which common knowledge of technologists is not recorded in that reference, since amino acid sequence, such as that for proinsulin, is within experts' common knowledge once it is finally determined and widely reported within literature of discipline, even if experts have not memorized such formula, and since human proinsulin sequence in question was reported in reference work and other literature in relevant discipline.

PATENTS
**[7] Patentability/Validity -- Anticipation -- Identity of elements (Section 115.0704)**
Prior art patent is enabling for human proinsulin cDNA sequence in context of anticipation analysis, even though it did not include specific human proinsulin amino acid sequence, since extrinsic evidence is admissable to explain disclosure of reference in situations in which common knowledge of technologists is not recorded in that reference, and since evidence shows that correct human proinsulin sequence was reported with certainty in literature of discipline and was therefore within common knowledge of those skilled in art well before publication date of prior patent; broad claims of patent for transfer vector and microorganism containing human proinsulin genes, if not limited to direct expression of human proinsulin, would therefore have been anticipated by prior patent.

PATENTS
**[8] Practice and procedure in Patent and Trademark Office -- Prosecution -- Duty of candor -- In general (Section 110.0903.01)**
Concept of inequitable conduct is not limited to situations in which patent applicant intentionally misleads Patent and Trademark Office in context of prior art, but rather may be found in variety of circumstances in which patent applicant has abandoned duty of candor, good faith and honesty to PTO.

PATENTS
**[9] Practice and procedure in Patent and Trademark Office -- Prosecution -- Duty of candor -- Materiality (Section 110.0903.04)**
**Infringement Defenses -- Fraud or unclean hands (Section 120.1111)**
Patent for recombinant bacterial plasmids containing coding sequences of insulin genes is unenforceable for inequitable conduct, since certain data found in patent resulted from experiment conducted using plasmid that was not certified for use by National Institutes of Health at time of experimentation, since plaintiff reported use of different plasmid for data in issue to PTO examiner, since there is substantial likelihood that reasonable examiner would have considered plaintiff's unauthorized use of plasmid important in patentability determination, in that examiner could easily have determined that patent would not have acquired its filing date without use of unauthorized plasmid and data therefrom, since plaintiff's failure to reveal unauthorized use of plasmid was intentional, and since that intentional failure was meant to deceive or mislead examiner.

PATENTS
**[10] Practice and procedure in Patent and Trademark Office -- Prosecution -- Duty of candor -- Materiality (Section 110.0903.04)**
**Infringement Defenses -- Fraud or unclean hands (Section 120.1111)**
Plaintiff's failure to cite European patent

application to Patent and Trademark Office renders patent for transfer vector and microorganism containing human proinsulin genes unenforceable for inequitable conduct, since uncited reference, which describes application of DNA synthesis techniques to human proinsulin DNA in single plasmid and includes claim to plasmid containing human proinsulin made in this fashion, was not merely cumulative, since plaintiff, in course of prosecuting foreign counterparts to patent in suit, clearly became aware of European application's materiality, and since plaintiff's arguments countering intent to mislead are insufficient to overcome European application's high level of materiality and evidence that plaintiff knew of that materiality.

**PATENTS**
**Particular patents -- Chemical -- Recombinant DNA**
4,431,740, Bell, Pictet, Goodman, and Rutter, DNA transfer vector and transferred microorganisms containing human proinsulin and pre-proinsulin genes, unenforceable and not infringed.
4,652,525, Rutter, Pictet, Chirgwin, Goodman, Ullrich, and Shine, recombinant bacterial plasmids containing the coding sequences of insulin genes, invalid, unenforceable, and not infringed.

***1226** Action by the University of California against Eli Lilly and Co. for patent infringement, one of six cases, consolidated for pre-trial proceedings by Judicial Panel on Multidistrict Litigation under MDL docket no. 912, arising out of research arrangements and license agreements among University of

***1227** California, Genentech Inc., and Eli Lilly and Co. Judgment for defendant. Prior decision: 34 USPQ2d 1097 .

Arthur I. Neustadt, Jean-Paul Lavalleye, Marc R. Labgold, and William J. Healey, of Oblon, Spivak, McClelland, Maier & Neustadt, Arlington, Va.; Susan B. Tabler, of Ice, Miller, Donadio & Ryand, Indianapolis, Ind.; Gerald P. Dodson and Emily A. Evans, of Arnold, White & Durkee, Palo Alto, Calif., for plaintiff.

Donald R. Dunner, Charles E. Lipsey, and Mark W. Lauroesch, of Finnegan, Henderson, Farabow, Garrett & Dunner, Washington, D.C.; Jerry E. Hyland and Jan M. Carroll, of Barnes & Thornburg, Indianapolis; Amy E. Hamilton, Indianapolis, for Eli Lilly & Co.

John E. Kidd and Maurice N. Ross, of Rogers & Wells, New York, N.Y.; Hugh E. Reynolds Jr. and David T. Kasper, of Locke, Reynolds, Boyd & Weisell, Indianapolis, for Genetech Inc.

Dillin, S.J.

Heretofore, from August 21 through September 1, 1995, the Court heard a bench trial of this action. Post-trial briefs were filed in lieu of closing arguments, the last of which were filed October 27, 1995. Having heard the evidence, considered the briefs, and being duly advised, the Court now makes its findings of fact and conclusions of law in the form of this Memorandum of Opinion.

*Background*

This case was initiated when the Regents of the University of California (UC) filed a patent infringement action against Eli Lilly and Company (Lilly) on February 7, 1990, in the United States District Court for the Northern District of California. UC's Amended Complaint, filed on April 24, 1991 alleges that Lilly's production of recombinant DNA human insulin products willfully infringes three of UC's patents: United States Patent Numbers 4,652,525 (the '525 patent); 4,431,740 (the '740 patent); and 4,440,859 (the '859 patent). After filing its Amended Complaint, UC withdrew its infringement charges arising from the '859 patent, leaving the '525 and the '740 patents at the center of this dispute.

In early 1992, the instant action was one of six cases consolidated in this Court for pretrial proceedings by the Judicial Panel on Multidistrict Litigation. *See In re Recombinant DNA Technology*

*Patent and Contract Litig.*, Docket No. 912 (J.P.M.L. Feb. 19, 1992), *aff'd, In re Regents of the Univ. of Cal.*, 964 F.2d 1128 [ 22 USPQ2d 1748 ] (Fed. Cir. 1992); *In re Recombinant DNA Technology Patent and Contract Litig.*, Docket No. 912 (J.P.M.L. Oct. 1, 1993). During the discovery stage of this and the other consolidated actions and on Lilly's motion, this Court transferred cause number IP-92-0224-C to the Southern District of Indiana pursuant to 28 U.S.C. Section 1404(a).

The '525 patent issued to UC on March 24, 1987, for an invention entitled, "Recombinant Bacterial Plasmids Containing the Coding Sequences of Insulin Genes." The named inventors on the patent are Dr. William J. Rutter (Rutter), Dr. Raymond Pictet (Pictet), Dr. John Chirgwin (Chirgwin), Dr. Howard Goodman (Goodman), Dr. Axel Ullrich (Ullrich) and Dr. John Shine (Shine). The '740 patent issued to UC on February 14, 1984, for an invention entitled, "DNA Transfer Vector and Transformed Microorganism Containing Human Proinsulin and Pre-proinsulin Genes." The named inventors on the '740 patent are Dr. Graeme Bell (Bell), Pictet, Goodman and Rutter. Although the '740 patent issued prior to issuance of the '525 patent , the '525 bears an earlier application date than does the '740.

As their titles reflect, the patents in issue in this case involve recombinant DNA technology. Recombinant DNA is "DNA that has been artificially introduced into a cell so that it alters the genotype and phenotype of the cell and is replicated along with the natural DNA." [FN1] Following is a brief review of the science involved in recombinant DNA technology.

All living things are composed of cells, which can be thought of as microscopic, biological building blocks. Deoxyribonucleic acid (DNA), in various compositions, is found in all living cells. In higher organisms known as eukaryotes, such as humans, DNA is contained within the nucleus of the cell. In lower organisms known as prokaryotes, such as bacteria and algae, DNA is found in the cytoplasm of the cell.

The DNA molecule contains, in effect, coded instructions for the manufacture of chemicals necessary for life, including proteins such as insulin and growth hormone in humans. The molecular structure of DNA is in the form of a double helix, generally conceptualized as an enormously long, twisted ***1228** rope ladder. The length and specific structure of DNA corresponds to the complexity of the organism. It is estimated that the human DNA ladder contains several billion "rungs."

Each rung of any DNA molecule consists of a pair of base chemicals (or nucleotides), of which there are only four used to build up DNA molecules -- adenine, thymine, guanine and cytosine. In large part, the varying pattern of these chemicals gives each complete DNA molecule its uniqueness. In addition, each rung in the DNA molecule contains a joint, thereby enabling a rung to be broken by the cell and reattached. Thus, a cell can duplicate its DNA or copy small sections of it.

A section of DNA that contains the coded instructions for the manufacture of a particular protein is called a gene. When the information contained in a particular gene is communicated to other parts of the cell, the cell can produce that protein encoded in the gene.

Scientists have discovered that the form of information in DNA is not unique to a particular species. For example, single cell bacteria can read sections of human DNA when such DNA sections are attached to the bacteria's own DNA and then can produce the chemicals encoded therein.

Molecular biologists and chemists only recently have developed the techniques necessary to isolate a particular human gene, determine its sequence, i.e., its structure, copy or synthesize it, insert it into the DNA of bacteria, and coax the bacteria to follow the gene's directions and express the desired chemical. Since bacteria replicate very rapidly and the altered DNA of the bacteria is duplicated in the replication process, the production of the desired chemical by bacteria has become commercially feasible.

Significant to this case are three methods for obtaining genes for use in the recombinant production of a desired protein -- in this case, human proinsulin and, ultimately, human insulin. In the first method, messenger RNA (mRNA) is derived from human tissue that produces insulin and subsequently is subjected to a process called reverse transcription. [FN2] Through reverse transcription,

copy (or complementary) DNA (cDNA) is obtained, mirroring the DNA encoding proinsulin found in the human source. A second method for obtaining a gene entails a chemical process and results in an artificial (or synthetic) gene. The artificial gene is made in test tubes (*in vitro*) using a series of repetitive chemical reactions to build up a desired DNA sequence. This desired sequence is determined in advance based on the protein sequence (sequence of amino acid building blocks) of the material one wants the cell to produce. The third method of obtaining a gene involves a combination of the cDNA and artificial DNA methods. Its product is referred to as semisynthetic DNA. [FN3]

The gene Lilly uses in manufacturing human proinsulin is a semisynthetic segment of DNA. UC contends that Lilly's use of this proinsulin gene in its commercial production of human proinsulin -- a precursor to the protein human insulin used in the treatment of diabetes -- infringes the '525 patent under the doctrine of equivalents and infringes the '740 patent both literally and under the doctrine of equivalents. Lilly counters not only that it is infringing neither of UC's patents, but also that both the patents are invalid and unenforceable. We will consider such issues in the order named.

I. *Infringement*

An infringement analysis is a two-step process. First, the court must determine the meaning and scope of the patent claims allegedly infringed. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 [ 34 USPQ2d 1421 ] (Fed. Cir.) (citation omitted), *cert. granted*, 116 S. Ct. 40, 132 L. Ed. 2d 921 (1995) . This step is often referred to as claim construction or claim interpretation. *Id.* Next, the properly construed claims must be compared to the product or process accused of infringing. *Id.*

UC's charges against Lilly include both literal infringement and infringement under the doctrine of equivalents. UC must prove infringement by a preponderance of the evidence. *Braun, Inc. v. Dynamics Corp. of America*, 975 F.2d 815, 819 [ 24 USPQ2d 1121 ] (Fed. Cir. 1992). Literal infringement is established if each and every element of the claim is present in the accused article. *Laitram Corp. v. Rexnord, Inc.*, 939 F.2d 1533, 1535 [ 19 USPQ2d 1367 ] (Fed. Cir. 1991).

Moreover, courts long have applied the doctrine of equivalents to protect the substance of the patentee's right to exclude. ***1229***Hilton Davis Chemical Co. v. Warner-Jenkinson Co., Inc.*, 62 F.3d 1512, 1517 [35 USPQ2d 1641] (Fed. Cir. 1995), *petition for cert. filed*, 64 U.S.L.W. 3349 (U.S. Nov. 6, 1995) (No. 95-728). In order to avoid infringement under the doctrine of equivalents, an accused product or process "must include 'substantial and not merely colorable' differences from the patent claims."*Id.* (quoting *Singer Mfg. Co. v. Cramer*, 192 U.S. 265, 286 (1904) (further citations omitted)). In *Hilton Davis*, the Federal Circuit held that the "application of the doctrine of equivalents rests on the substantiality of the differences between the claimed and accused products or processes, assessed according to an objective standard."*Id.* at 1518.

The Federal Circuit has stated that the traditional function-way-result test [FN4] is one measure of the substantiality of the differences between the patented and accused products or processes. However, the court explained, " 'equivalence, in the patent law, is not the prisoner of a formula. . . .' " *Hilton Davis*, 62 F.3d at 1518 (quoting *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 609 [ 85 USPQ 328 ] (1950)). The court admonished that the finder of fact must consider *all* evidence relevant to the substantiality of the differences whether or not such evidence is pertinent to the function-way-result test. *Id.* at 1518-20. The court discussed evidence of copying and evidence of designing around and stated that such evidence may be relevant to the issue of infringement under the doctrine of equivalents. *Id.*

A. *The '525 Patent* At issue are independent claims one and two of the '525 patent and dependent claims four through seven. In claim one, the inventors claim:

A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

UC Ex. 2 at col. 20. Claim two is similar to claim one, but rather than claiming the recombinant plasmid, [FN5] it claims the microorganism that contains the recombinant DNA. *Id.* at col. 21.

The parties agree that the claims in the '525 describe cDNA, a description embodied in the phrase "reverse transcript of an mRNA." Since Lilly's proinsulin DNA sequence is a semisynthetic sequence rather than cDNA, UC does not allege that Lilly literally infringes the claims of the '525 patent. UC does assert, however, that Lilly's DNA infringes under the doctrine of equivalents. Hence, we must consider if there exist only insubstantial differences between the subject claims of the '525 and Lilly's DNA. The answer becomes clear when we look further into the meaning and scope of the claims of the '525 patent. The language of the '525 patent and trial testimony convince us that the proper meaning and scope of the '525 claims prevent UC from prevailing in its contention that Lilly's plasmid infringes the '525 patent under the doctrine of equivalents. We explain.

In trial, Lilly established that approximately the first third of the proinsulin-encoding sequence contained in its plasmid is synthesized chemically. Lilly uses this chemically synthesized portion so that its proinsulin-encoding sequence begins precisely at the first amino acid for human proinsulin. Tr. at 1390-91. The technique of providing such a precise starting point is called tailoring. Lilly's expert Dr. Walter Gilbert [FN6] (Gilbert) testified that the techniques described in the '525 patent do not disclose tailoring techniques. Tr. at 1391, 1394. Gilbert further averred that he was unaware of any cDNA cloning [FN7] experiments using the technology revealed in the '525 patent yielding a piece of cDNA starting precisely at the beginning of the proinsulin-encoding sequence. Tr. at 1398. The evidence indicates that all cloned cDNAs ***1230** during the relevant time period were either too long or too short to encode human proinsulin precisely.

Moreover, in the prosecution of another of UC's Patents -- the '740 patent, which bears a file date later than that of the '525 -- UC representatives argued to the United States Patent and Trademark Office (PTO) examiner that

> prior art cloned cDNAs, such as disclosed by the cited references, have not provided defined precise starting points but have instead been either too long, comprising 5 ' untranslated regions, [FN8] or too short, being fragments of the desired sequence. No techniques for tailoring cloned cDNAs to provide a defined starting point have been disclosed in the prior art.
>
> Lilly Ex. 3029E at A000176-77.

The cited references to which this quoted passage refers includes a paper by Ullrich and other scientists (Ullrich *et al.*) published in *Science* on June 17, 1977. The PTO examiner's citation of the Ullrich *et al.* paper is particularly relevant to this discussion because that paper provides the basic disclosure for the specification of the '525 patent. Indeed, Gilbert testified that "the '525 patent doesn't reveal any technique that is not revealed in the Ullrich publication; and therefore, provides no technique to provide a defined end." Tr. at 1394; *see also* tr. at 561. UC's argument during prosecution of the '740 patent, quoted above, was an effort to prevent rejection of certain claims in the '740 patent based on lack of novelty or obviousness in light of, among other references, the Ullrich *et al.* paper. Such argument is telling evidence of UC's position concerning the disclosure of the '525 patent . It is obvious that even UC believed that the '525 patent did not disclose the tailoring techniques presently in issue. Indeed, the PTO examiner's eventual decision to issue certain of the claims in the '740 patent was based on his determination that the human proinsulin-encoding sequences contained in those claims were tailored, rendering them patentable over the prior art. UC Ex. 3 at A000172, A000254.

UC's argument countering Lilly's position is unpersuasive. Trial testimony indicated that use of the cloning method described in the '525 patent would yield molecules of a variety of lengths. Tr. at 722, 1472. From this, UC attempted to establish that within this array of molecules would be that one molecule beginning precisely at the starting point for human proinsulin. Gilbert, however, testified that although the possibility existed that one could find the molecule with the precise starting point, the possibility is rather low. Tr. at 1473. " [T]hat molecule may be there, and it, in fact, may not be there. It may be there at one part in a million or one part in a billion." Tr. at 1473. Moreover, UC's expert Dr. John Richards (Richards) testified that he was unaware of any experiments using the technology in the '525 patent or the Ullrich *et al.* paper that resulted in a molecule starting precisely at the beginning of the proinsulin sequence. Tr. at

724.

[1] The Court is not convinced that a DNA sequence specifically tailored to a precise beginning infringes a patent that fortuitously carries with it an unlikely possibility that a scientist, using the methods of the patent, may locate a cDNA having a precise starting point. For these reasons and in the wake of another examination of the language of the '525 patent, we find that the '525 patent, properly interpreted, fails to provide the tailoring techniques necessary to enable one skilled in the art to prepare a coding sequence whose starting point corresponds precisely with the first amino acid for human proinsulin. Because the specification does not so provide, we find that the claims cannot be read to encompass plasmids and microorganisms containing tailored coding sequences.

Significant to our decision, we do not believe that a plasmid made by the method of the '525 patent either would perform in substantially the same way or result in the same product as would a plasmid containing a tailored coding sequence such as the one Lilly uses. Specifically, Gilbert testified that use of a sequence that was either too long or too short to encode proinsulin precisely would not work in Lilly's system. Tr. at 1390-91. He averred that Lilly's system requires use of a plasmid that contains an insert encoding the exact amino acid sequence for human proinsulin. *Id.*

The '525 patent does not disclose such a plasmid or an equivalent thereof. Moreover, Lilly expert Robert Armitage (Armitage) testified that Lilly's plasmid makes substantial molecular departures from the natural cDNA sequence provided in the '525 patent. Tr. at 1859. The differences include, but are not limited to, the removal of the "first 100 nucleotide bases of the natural sequence and [substitution of] a synthetic sequence that has on the order of 20 changes from the natural sequence which would be the sequence represented for human cDNA had that structure actually been available and ***1231** included in the '525 patent." [FN9] Tr. at 1859. Consequently, we find that Lilly does not infringe the subject claims of the '525 patent under the doctrine of equivalents.

B. *The '740 Patent*

UC alleges that Lilly's accused plasmid both literally infringes the '740 patent and infringes under the doctrine of equivalents. We will begin by addressing UC's allegations of literal infringement. UC contends that Lilly literally infringes claims five, six and eight through ten of the '740 patent.

1. *Literal Infringement*

a. *Claims five and six* [FN10] Claims five and six claim:

5. A DNA transfer vector comprising a deoxynucleotide sequence coding for human proinsulin consisting essentially of a plus strand having the sequence:

[selected from among all possible DNA sequences encoding human proinsulin).

6. A microorganism transformed by the transfer vector of claim 4 or 5.

UC Ex. 1 at cols. 17-18.

Previously, UC moved the Court for summary judgment on Lilly's alleged literal infringement of claims five and six of the '740 patent. In response to UC's motion, Lilly argued that its use of a fusion protein precluded UC from succeeding with its literal infringement charge. We denied UC's motion, explaining that it was necessary for us to obtain more information before we could discharge our duty of claim interpretation.

The DNA that Lilly employs in its recombinant production of human insulin is a fusion protein consisting of three parts: a bacterial protein, a methionine residue and a semisynthetic proinsulin-encoding sequence. Lilly's DNA is referred to as a fusion protein because, in essence, the three parts are fused together in order ultimately to produce the desired proinsulin. The function of the bacterial protein preceding the methionine and the proinsulin-encoding sequence is to protect the desired product from degradation. The methionine residue is inserted between the bacterial protein and the proinsulin-encoding sequence. It provides a cleavage point such that after the DNA is inserted into a plasmid, that, in turn, is inserted into a bacterium for production of the fusion protein, the bacterial portion of the fusion protein can be

cleaved (or removed) from the human portion. [FN11]

Having now heard all the evidence, the Court again has examined the prosecution history of the '740, its specification and its claims, and has heard experts on the matter at hand. In light of this evidence, we find that Lilly's use of a fusion protein in its production of human (pro)insulin prevents Lilly from literally infringing claims five and six of UC's patent.

Several factors indicate that a fusion protein encoding for human proinsulin cannot literally infringe claim five of the '740 patent. The prosecution history illustrates that the PTO examiner believed that DNA transfer vectors containing human proinsulin fusion proteins were in the prior art. [FN12] We ***1232** agree with his assessment. The Ullrich *et al. Science* article and the Villa-Komaroff *et al.* article disclose the cloning of rat insulin cDNA. In his first rejection of the '740 patent application, the examiner stated that, in light of the prior art, it would be obvious to prepare human insulin genes rather than rat insulin genes. UC Ex. 3 at A000142.

In an attempt to overcome the examiner's initial rejection of the claims, UC argued that the prior art cited against the '740 patent application did not teach

essential aspects of the method of preparing the claimed compounds or compositions. Furthermore, the compounds themselves have unobvious structural and functional properties not taught, suggested or predictable from the prior art.

UC Ex. 3 at A000154.

The PTO examiner disagreed. He first reiterated his rejection based on the Ullrich and Villa-Komaroff articles and the articles' disclosure of the cloning of rat insulin cDNA. Significantly, he continued his rejection rationale, stating that Ullrich and Villa- Komaroff "suggest that their *processes* should be applicable to the expression of any eukaryotic protein including human insulin." UC Ex. 3 at A000166 (emphasis added). The page citations the examiner provides for the Ullrich and Villa-Komaroff process references correspond to discussions in those articles concerning fusion protein processes.

For example, the examiner refers the applicant to page 3730, column two of the Villa-Komaroff *et al.* article, an article that plainly discusses the expression of a fusion product. At the examiner's pinpoint cite, the authors are discussing fusion proteins. Significantly, in column two the authors assert, "Clearly we have exploited a general method that should lead to the expression and secretion of any eukaryotic protein provided another protein, such as penicillinase, will serve as a carrier, by virtue of its leader sequence." Lilly Ex. 3182 at 3730. Indeed, Lilly's experts Dr. Robert Old (Old) and Armitage testified that the Villa-Komaroff *et al.* article describes the production of fusion protein DNA sequences. [FN13] Tr. at 1618-19, 1628, 1799.

In his rejection, the PTO examiner also cites to specific pages in the Ullrich *et al. Symposium* paper. On one of those pages, the authors state:

Because of the differences between eukaryotic and prokaryotic transcriptional and translational regulatory elements, it is necessary to combine the genetic information for the eukaryotic insulin gene with prokaryotic regulatory sequences, to obtain expression of insulin in bacteria. . . .

Two plasmids have been constructed, in which the insulin DNA fragment is fused to different length portions of the gene for B-galactosidase, the first gene in the lactose operon. . . .

Lilly Ex. 3180 at 24. The authors further relate that although they had no success when fusing the protein to a short segment of the B-galactosidase gene, yet the desired protein was detected wherein the rat insulin gene was fused to a longer portion of the B-galactosidase gene. *Id.* In fact, Old testified that the *Symposium* article "describes expression and attempt at expression of a short fusion and a long fusion in bacteria." Tr. at 1618. The examiner also made reference to page 26 of the article. The authors discuss the success they had in employing the longer portion of the B-galactosidase gene and suggest that "it is possible that the large bacterial portion of the fusion product protects the insulin polypeptide from cellular protease degradation." Lilly Ex. 3180 at 26.

Finally, although the PTO examiner does not cite the Crea *et al.* article in his argument pertaining to fusion processes at this point, that article also describes use of fusion proteins in the production of human insulin through chemical synthesis of the A and B insulin chains separately. Crea *et al.* fused the genes for the A and B chains of insulin to the *E. coli* B-galactosidase gene. *See* Lilly Ex. 3100; *see also* tr. at 1616-17.

As we stated previously, we agree with the examiner's determination that the prior art encompassed human proinsulin fusion proteins. We are even more convinced when we add to the prior art a publication that UC failed to bring to the attention of the PTO examiner -- European Patent Application ***1233** 1929 (EPA-1929). [FN14] Lilly Ex. 3047 at 42. In sum, the record indicates that the prior art contained a number of references to the use of fusion proteins -- not only for the production of human proinsulin, but also for the expression of any eukaryotic protein.

Our interpretation of claim five is supported by other portions of the prosecution history. Following the PTO examiner's rejection of the claims in the '740 patent application, a UC representative had a personal interview with the examiner and, subsequently, the examiner completed an interview summary record. In it, the examiner stated:

Will limit claims to DNA transfer vector containing only the tailored starting point [of] human proinsulin and preproinsulin as for example as recited in claim 5. If so properly limited will allow since references do not show or contemplate that feature.

UC Ex. 3 at A000172.

In response to the examiner's comment, UC submitted an amendment to claim two. As originally submitted, claim two read: "A DNA transfer vector comprising a deoxynucleotide sequence coding for human proinsulin." UC Ex. 3 at A000036. UC's amended claim two claimed:

A DNA transfer vector comprising *an inserted cDNA having* a deoxynucleotide sequence coding for human proinsulin [.] , *the plus strand of said cDNA having a defined 5 'end, said 5 'end being the first deox* y *nucleotide of the sequence coding for said proinsulin.*

UC Ex. 3 at A000173-74. With this amendment, UC narrowed the focus of claim two to tailored human proinsulin cDNA. In its previous claim two language, UC had encompassed all sequences coding for human proinsulin, whether or not the nucleotide sequence mirrored that found in the natural source -- in this case, the human -- and whether or not the cDNA was tailored.

Accompanying the amendment were UC's remarks in further support of patentability. UC reasoned that the examiner fully had not considered that its invention involved more than the cloning of cDNA for human proinsulin. UC contended that the invention

also includes additional modifications of the cloned cDNA. Such modifications are termed "tailoring", since they involve a custom-designed sequence of reactions to remove specific portions of the 5 ' region of the cDNA, yielding transfer vectors in which the human cDNA moiety has a specific defined starting point. Two such defined starting points disclosed herein include the start of the preproinsulin coding segment and the start of the proinsulin coding segment. The claims have been amended to more particularly point out and distinctly claim the invention with respect to the tailoring aspect.

The invention herein is perceived as including a novel and unobviously attainable structural feature, namely a defined starting point at the 5 ' end (relative to the plus strand of the cDNA). Such defined starting points are obtained by complex and individualized "tailoring" reactions. Such tailoring reactions are designed to specifically remove portions of the 5 ' end of the plus strand of cloned cDNA to yield a cloned cDNA having a defined 5 ' start point different from that originally cloned. . . .

UC Ex. 3 at A000175. UC did not submit an amendment for claim five -- another claim originally encompassing all DNA sequences encoding human proinsulin.

The examiner considered UC's amendment and remarks and rejected all claims. Subsequently, UC's appeal of the examiner's decision, the notice of which was lodged in May of 1982, was dismissed,

apparently because UC failed to file a brief. On June 8, 1982, UC filed a continuation of the same patent application accompanied by a preliminary amendment. That preliminary amendment included, *inter alia*, a further amendment to claim two. This amendment changed the phrase that previously read "an inserted cDNA having" to "an inserted cDNA consisting essentially of." UC Ex. 3 ***1234** at A000248. Again, UC offered no change to claim five.

Following this second proffered amendment, the examiner conducted a telephone interview with UC in which claims two and five, among others, were discussed, as was the prior art of Ullrich *et al.*, Villa-Komaroff *et al.* and Crea *et al.* *See* UC Ex.3 at A000252. After the interview, the examiner completed a notice of allowance of certain claims, including claims two and five. The claims were allowed in view of the examiner's amendment to the record. The examiner's amendment encompassed not only the language change included in UC's second amendment to claim two, but also a change in the language of claim five. Originally, claim five claimed:

A DNA transfer vector comprising a deoxynucleotide sequence coding for human proinsulin comprising a plus strand having the sequence:

[selected from among all the possible DNA sequences coding for human proinsulin].

UC Ex. 3 at A000037. The examiner's amendment stipulated that UC change its second use of the word "comprising" in claim five to the phrase "consisting essentially of," [FN15] so that the claim now reads:

A DNA transfer vector comprising a deoxynucleotide sequence coding for human proinsulin consisting essentially of a plus strand having the sequence:

[selected from among all the possible DNA sequences coding for human proinsulin].

*Id.* at A000254. His reasons for allowing the claims to issue, as amended, were as follows:

The claims are deemed to define over the prior art for substantially the reasons advanced in the amendment filed April 5, 1982 (paper No. 19) of parent application Serial No. 075,192 and because the examiner's amendment excludes from the cDNA the presence of sequences other than proinsulin or preproinsulin.

*Id.* The examiner told UC that should the changes be unacceptable, UC had the option of filing an amendment pursuant to 37 C.F.R. 1.312 (Rule 312 amendment).

UC urges the Court to find that the examiner's mandated amendment and reasons therefore illustrate that he was excluding from the claims in issue only naturally occurring sequences -- an exclusion, UC argues, that does not encompass the substances preceding Lilly's proinsulin-coding sequence. UC points to the examiner's use of the acronym "cDNA" when he cited his reasons for the mandated amendment. Since cDNA refers only to the DNA sequence found in the natural source, UC contends, the examiner's exclusion only prevents the patented claims from including substances that naturally occur upstream from the proinsulin-encoding sequence.

Lilly contends, however, that the examiner's mandated amendment is proof that claim five cannot be interpreted as covering fusion proteins. Lilly first focuses on the examiner's addition of the phrase "consisting essentially of" to claim five. This phrase, Lilly argues, precludes the claims in issue from encompassing a vector with an inserted DNA sequence containing *any* elements upstream from the tailored starting point of human proinsulin. Lilly asserts that the examiner's agreement with this position is illustrated in the first interview summary record where he stated that the claims would be allowed if UC limited them to DNA transfer vectors containing "*only* the tailored starting point [of] human proinsulin and preproinsulin. . . ." UC Ex. 3 at A000172 (emphasis added). In response to UC's argument that the examiner's use of the acronym "cDNA" indicates alliance with UC's camp, Lilly reasons that his use of the acronym was merely a misnomer. Lilly asserts that the examiner's notes from both interviews with UC must be read together in order accurately to determine the examiner's intent, and that such a ***1235** reading illustrates that the examiner intended to exclude fusion proteins from claim five. An examination of the amendments

to claims two and five and trial testimony, as well as our earlier perusal of the prior art, persuade us that Lilly's position is well taken. First, the examiner's initial summary record unambiguously supports Lilly's position. In that record, the examiner states that he will allow the subject claims if UC structures those claims to encompass transfer vectors containing *only* the tailored starting point of human proinsulin. In response, UC amended only claim two and did so in such a fashion that, if accepted, it undoubtedly would have encompassed human proinsulin fusion proteins. Tr. at 1797. UC's use of the phrase "an inserted cDNA *having* a deoxynucleotide sequence . . .,"*id.* (emphasis added), would have meant that UC's insert not only would have a cDNA sequence coding for human proinsulin, but also could have other unenumerated sequences -- for example, a fusion protein. Thus, in this state, claim two encompassed use of a fusion protein to produce human proinsulin via a tailored cDNA. The examiner, however, did not accept UC's proffered amendment. When the matter came before the examiner again, UC had replaced claim two's phrase "an inserted cDNA having" with "an inserted cDNA consisting essentially of." We find that this version of the claim not only retained the claim's limitation of a tailored cDNA, but also further restricted the claim to direct expression by employing use of the nearly closed-ended phrase "consisting essentially of." Still, UC had not amended claim five. In its unaltered state, claim five certainly would have encompassed fusion proteins. However, before the examiner would allow claim five to issue, he mandated that the limiting language be added. Thus, claim five as issued covers transfer vectors that include a DNA sequence coding for human proinsulin *consisting essentially of* any of the sequences that code for that protein. We conclude that the examiner's addition of the phrase "consisting essentially of" is additional proof that he believed human proinsulin fusion proteins were not patentable to UC. By mandating use of the limiting language, the examiner strategically excluded fusion proteins from UC's claims. We further conclude that the examiner intended to use the acronym "DNA" rather than "cDNA" in his reasons for allowing the claims finally to issue. This reading not only is consistent with the mandated claim language and the prior art, but also takes into consideration claim five's focus on the trillions of DNA sequences that are not identical to the cDNA sequence.

Furthermore, Armitage pointed out yet another excerpt from the prosecution history of the '740 patent that suggests the examiner meant "DNA" when he used the term "cDNA" in his statement of reasons for allowing the subject claims to issue. Specifically, in the examiner's statement, he said that the claims define over the prior art for the reasons advanced in UC's April 5, 1982, amendment and because his amendment -- the amendment now in issue -- excludes from the cDNA the presence of sequences other than proinsulin. UC Ex. 3 at A000254. In UC's April 5, 1982, amendment, UC contended that its claims were patentable over the prior art largely because of the tailoring aspect -- that is, the removal of specific portions of the cDNA to yield a defined starting point. UC Ex. 3 at A000174-77. If UC's argument were correct and the examiner actually meant only cDNA when he used that term, the examiner's reasons for allowance would be redundant; he would be reasoning that the claims define over the prior art because the cDNA is tailored (as articulated in UC's April 5, 1982, amendment) and because the cDNA is tailored (as UC would have the Court interpret the examiner's reference to cDNA). We are persuaded that this was not the examiner's intent.

Finally, we turn to another portion of the prosecution history supporting our conclusion that fusion proteins literally cannot infringe claims five or six of the '740 patent. We earlier noted that in his amendment to the patent claims, the examiner informed UC that if the changes he mandated were unacceptable, UC could file a Rule 312 amendment. UC apparently was not satisfied with the examiner's amendment. On June 23, 1983, UC filed a Rule 312 amendment in an attempt, UC reasoned, "to include in each of the claims linkers, poly-G-C tails or other connectors attached to either side of each sequence in question." UC Ex. 3 at A000264. UC described the additions as "trivial." In the Rule 312 amendment, UC requested, *inter alia*, the following revisions to claims two and five:

2. (Thrice Amended) A DNA transfer vector comprising an inserted *DNA comprising a* cDNA consisting essentially of a deoxynucleotide sequence coding for human proinsulin, the plus strand of said cDNA having a defined 5 ' end, said 5 ' end being the first deoxynucleotide of the sequence coding for said proinsulin.

. . . ***1236** Claim 5, first three lines, should read as follows:

5. (Twice Amended) A DNA transfer vector comprising *an inserted DNA comprising* a *plus strand* [deoxynucleotide sequence] *consisting essentially of the deoxynucleotide sequence* coding for human proinsulin, *said sequence* [consisting essentially of a plus strand] having the sequence:

UC Ex. 3 at A000263. If UC's amendment had been accepted, the claims clearly would have brought fusion proteins within their purview. The examiner, however, did not deem the additions trivial. In fact, he found that UC's proposed Rule 312 amendment raised new issues of scope and support and denied UC's request to amend. UC Ex. 3 at A000265. This denial provides yet another indication that the examiner believed that human proinsulin fusion proteins were not patentable to UC. We concur in his conclusion. Also significant to this discussion is the divisional application UC filed October 24, 1983, stemming from the application that matured into the ' 740 patent and having the same specification. Lilly Ex. 3030 at OFW 776. Early in the prosecution of the '740 patent application, the examiner informed UC that its patent claims were directed to more than one invention and, therefore, stipulated that UC restrict its claims accordingly. Eventually, the claims directed to fusion proteins -- original claims twelve and thirteen -- were determined to be distinct claims such that they could support a separate patent. *See* UC Ex. 3 at A000134-142. UC chose to prosecute claims one to eleven -- claims twelve through twenty-one, including the fusion protein claims, were withdrawn from consideration.

Later, in the aforementioned divisional application, UC again brought the fusion protein claims to the forefront, at which time the examiner rejected them as unpatentable. In his first rejection, the examiner asserted that a combination of Ullrich *et al.*, Villa Komaroff *et al.* and Crea *et al.* rendered obvious fused proteins for human proinsulin. *See* Lilly Ex. 3030 at OFW 791-92. In response, UC submitted an amendment in which it cancelled claims twelve and thirteen without prejudice and added new claims twenty-two through twenty- four. [FN16] In his rejection of these new fusion protein claims, the examiner found yet another reference upon which to base his rejection -- United States Patent Number 4,366,246 (the '246 patent). [FN17] Lilly Ex. 3030 at OFW 807. The examiner stated:

Riggs teach methods of preparing mammalian fusion proteins (human somatostatin and insulin) wherein the entire mammalian protein is fused at its C-terminus to the N-terminus of a procaryotic protein with an intermediate enzymatically cleavable segment joining the termini. . . . Further, while Riggs primarily chemically synthesizes his genes . . . prior to cloning and expression he also does embrace the use of cDNA genes resulting from reverse transcription from mRNA, and specifically those of Ullrich et al. It would be obvious to use the teaching of Riggs in the preparation of human proinsulin and preproinsulin as would result from the other combined references. Additionally it would be obvious to construct the insulin fusion proteins by conventional peptide chemistry.

*Id.* at OFW 807-08. Subsequently, UC abandoned its divisional application. *See* Lilly 3030 at OFW 822.

An examination of the language of claims twenty-two and twenty-four in UC's divisional application leads us to conclude that UC, itself, did not believe that it had captured human proinsulin fusion proteins in the '740 patent. Hence, UC attempted to do so in its divisional application. UC's attempt in 1986 to patent that which it now asserts is encompassed in the '740 patent lends further support to our interpretation of the claims in issue.

> [2] We find it prudent to address one last issue before concluding this literal infringement analysis. The issue involves the language ***1237** of claim fourteen, which claims a specific semisynthetic sequence coding for human proinsulin. Tr. at 1655-56. Amino acid position one of that sequence is preceded by the codon for methionine. *See* UC Ex. 1 at col. 20; tr. at 1827. At trial, it was suggested that claim fourteen's inclusion of a codon for methionine evidences the PTO examiner's willingness to grant fusion proteins to UC. We believe proper interpretation of claim fourteen dispels such a suggestion.

Armitage explained that methionine is a start codon; that is, a codon that "signals the cell that it's time to start producing protein from the DNA sequence." Tr. 1827. He opined that the fact that the

PTO examiner allowed UC to include this start codon in claim fourteen does not suggest that the examiner was permitting UC to claim fusion proteins. Tr. at 1827-28. The examiner, he testified, could have mandated the use of language prohibiting the use of this methionine codon, but that such mandate would have been "complete nonsense." Armitage reasoned that no substance can be expressed via the technology in issue without a start codon. *Id.* In fact, he averred that use of a start codon is "how direct expression takes place." Tr. at 1828. We find Armitage's testimony credible, we heard nothing to contradict his statements, and, thus, we do not believe that inclusion of a start codon in claim fourteen reflects that the examiner was granting fusion proteins to UC.

Moreover, we agree with Armitage's testimony concerning example 2A of the '740 patent's specification. In example 2A, the inventors describe use of a fusion protein. UC Ex. 1 at cols. 12-13. Further into the patent specification, the inventors in example 3 discuss expression both as a fusion product and through direct expression. *Id.* at cols. 15-16. As Armitage testified:

Well, the prior art references that the examiner applied taught fusion proteins but not direct expression. This patent teaches both fusion protein expression and direct expression; and therefore, the examiner found what he believed to be a basis for a patentable distinction of these claims over the references that he cited.

Tr. at 1829-30. We agree. Although UC attempted to garner both fusion protein expression and direct expression, the prosecution history of the '740 patent application indicates that it was successful only in its bid for direct expression claims. We are unconvinced that the inclusion of a start codon in claim fourteen signifies that UC's claims encompass fusion proteins.

[3] In conclusion, we believe the PTO examiner found that claim five was patentable only to the extent that it claimed vectors coding for the direct expression of human proinsulin, and we agree with his determination. As we discussed earlier, construction of a fusion protein was in the prior art, not only for (pro)insulin, but also for other proteins. Also significant to the Court's interpretation of claim five is our belief that the amino acid sequence for human proinsulin was in the prior art. [FN18] Consequently, the transfer vector patented in claim five is that which provides for direct expression of human proinsulin. Fusion proteins are excluded. For these reasons, Lilly's accused plasmid does not literally infringe claims five and six of UC's '740 patent.

b. *Claims eight, nine and ten*

UC also accuses Lilly of literal infringement of claims eight through ten of the '740 patent. In those claims, the inventors claim:

8. The plasmid pcHP-1.

9. A microorganism transformed by the plasmid of claim 7 or 8.

10. A microorganism as in claim 9 wherein the organism is *Escherichia coli.*

Claims nine and ten, to the extent they are involved in this action, are dependent on claim eight. As stated previously, the determination we reach regarding the independent claim applies with equal force to its dependent claims.

In the specification of the '740 patent, the inventors state that " [a] plasmid transfer vector comprising pBR322 with an inserted proinsulin coding sequence is designated pcHP-1." UC Ex. 1, col. 12 at lns. 49-51. In an effort to establish Lilly's infringement of claim eight, UC questioned expert Richards. Richards testified that he believes Lilly's plasmid infringes because it contains a pBR322 element with an inserted proinsulinencoding sequence. Tr. at 640-41.

Richards further testified that under his interpretation of claim eight, a plasmid already described in the prior art would fall within the scope of claim eight if a synthetic human proinsulin DNA sequence were substituted for the somatostatin DNA sequence actually described in that prior art. Tr. at 688-90. Significantly, the prior art to which Richards referred was EPA-1929, the published patent application earlier discussed in this Opinion, which, in claim six, claims a plasmid encoding a fusion protein for human proinsulin. Tr. at 687-691. If the Court were to interpret and validate claim

eight as broadly as UC suggests, claim eight would encompass the subject matter of claim six of ***1238** EPA-1929, which is prior art to the '740 patent.

The Court, however, does not interpret claim eight nearly so broadly as UC urges. To interpret claim eight as UC suggests would be to broaden the scope of the '740 patent far beyond that anticipated by the examiner as evidenced by the prosecution history. Indeed, UC's interpretation would give UC in claim eight sequences that the examiner clearly refused to give it in claims two and five. We conclude that claim eight, properly interpreted, requires that the proinsulin-encoding sequence inserted into the claimed plasmid, like those sequences in claims two and five, be a sequence coding for direct expression, i.e., not a fusion protein. Not only is this interpretation consistent with the prosecution history of the patent application, but also it is consistent with preexisting claim six of EPA-1929. In summary, we find that Lilly's plasmid does not literally infringe claims eight, nine and ten of UC's '740 patent. We now turn to the issue of infringement under the doctrine of equivalents.

2. *Infringement Under the Doctrine of Equivalents*

Our analysis does not end with a determination that there is no literal infringement of the subject claims. UC also alleges that Lilly's accused plasmid infringes claims two, three, thirteen and fourteen under the doctrine of equivalents. [FN19] Thus, we must determine if Lilly has made nothing more than "unimportant and insubstantial changes and substitutions in the patent which, though adding nothing, would be enough to take the copied matter outside the claim."*Graver Tank Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 607 [ 85 USPQ 328 ] (1950). We begin with an analysis of claim two of the '740 patent. [FN20]

UC's expert Richards testified that Lilly's plasmid infringes claim two of the '740 patent under the doctrine of equivalents. Tr. at 633. Richards stated that the human proinsulin encoding DNA sequence Lilly uses in its plasmid is not an identical copy of the cDNA. "There are some nucleotide changes," he averred. "But," he added, "in terms of function, they're insubstantial." Tr. at 634. Richards also testified that Lilly's plasmid -- like the transfer vector described in claim two of the '740 patent -- begins precisely at the first deoxynucleotide of the sequence coding for human proinsulin. Tr. at 635.

On cross examination, Richards stated that he could not remember the number of differences in nucleotides when comparing claims two and thirteen of the '740 patent to Lilly's accused plasmid. Tr. at 719. He opined that the differences were inconsequential because, in spite of the differences, the semisynthetic DNA sequence Lilly uses in its plasmid encodes human proinsulin. Tr. at 719.

> [4] The Court, however, is not so quick to disregard the differences. A determination of infringement by equivalence, even if we were to consider the facts of the case under the function-way-result test alone, requires more than consideration of the result -- in this case, human proinsulin. Rather, it also requires a comparison of function and way. Moreover, according to the Federal Circuit's decision in *Hilton Davis*, consideration of evidence of function- way-result may not be sufficient in every case. Specifically, a court must consider all the evidence relevant to the substantiality of the differences between the accused and patented products.

Even more important to the instant discussion is the proper scope of the subject claims. An examination of the language of claim two and thirteen, as well as the expert testimony at trial, establishes that claims two and thirteen are directed to the cDNA sequence. Specifically, the transfer vector that is claimed therein only encompasses the sequence of bases coding for proinsulin found in the human source.

***1239** According to Lilly's expert witness Old, there are twenty-four differences in the proinsulin nucleotide sequence between Lilly's plasmid construction and the cDNA claimed in claims two and thirteen of the '740 patent. Tr. at 1645; *see also* Lilly Ex. 4038 (asserting that there are 23 differences from the natural sequence). These differences convert Lilly's plasmid into one containing a DNA sequence that more nearly resembles a sequence described in UC's claim five -- the claim that encompasses all the possible DNA sequences for human proinsulin -- rather than the cDNA sequence described in claim two. Significantly, we earlier stated that the PTO examiner limited the scope of UC's generic claim

five to direct expression, i.e., expression of proinsulin without use of a fusion protein, and we agreed with the examiner's limitation. [FN21]

The Court is persuaded that it would be improper to broaden the scope of claims two, three and thirteen to give to UC that which the PTO examiner found unpatentable in the context of claim five. Hence, we find that Lilly's plasmid -- a plasmid that does not consist of the cDNA for human proinsulin -- does not infringe claim two, three or thirteen of the '740 patent. Furthermore, since Lilly's plasmid coding for human proinsulin utilizes the fusion protein concept, it cannot infringe claim five of the '740 patent.

Not only does claim thirteen's DNA sequence mirror that found in claim two, but also claim thirteen claims "the DNA transfer vector of claim 5. . . ." The language of claim fourteen does likewise. Such language renders claims thirteen and fourteen dependent on claim five. Tr. at 1827. We already have found that claim five is limited to direct expression and believe that claims thirteen and fourteen also properly are limited to direct expression. Hence, we reject UC's doctrine of equivalents argument.

II. *Invalidity*

Lilly asserts that certain claims, both in the '525 patent and in the ' 740 patent, are invalid. A patent is presumed valid, and the burden of establishing invalidity is on the challenger. *See* 35 U.S.C. Section 282; *see also American Hoist & Derrick Co. v. Sowa & Sons*, 725 F.2d 1350, 1358 [ 220 USPQ 763 ] (Fed. Cir. 1984). Furthermore, a court must be persuaded by clear and convincing evidence that the patent in issue is invalid. *American Hoist & Derrick Co.*, 725 F.2d at 1360. In the instant case, we first turn to address Lilly's contention of invalidity in the context of the '525 patent.

A. *The '525 Patent -- Written Description Requirement*

Lilly asserts that the '525 patent's claims to natural human proinsulin DNA are invalid under the first paragraph of 35 U.S.C. Section 112 because the inventors failed to provide the requisite written description of the claimed subject matter. [FN22] UC counters that the '525 patent sufficiently describes that which is claimed. UC states that the inventors of the '525 patent reduced to practice the rat insulin gene. According to UC, this reduction to practice entitled the inventors also to claim the genera of vertebrates and mammals of claims one, two, four, six and seven [FN23] -- genera of which the rat is a member. Additionally, UC contends, the inventors' accomplishment with rat cDNA, in conjunction with the method the '525 taught for isolating the insulin gene, permitted the inventors to capture the proinsulin cDNA of the human species as claimed in claim five. [FN24] UC adds that the isolation method taught in the '525 patent was that method it subsequently used actually to isolate the human proinsulin cDNA.

The statutory language in issue stipulates that

[t]he specification shall contain a written description of the invention, and of the manner and process of making and using ***1240** it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention. . . .

35 U.S.C. Section 112.

The legal standard for sufficiency of a patent's written description is whether that description " '. . . reasonably conveys to the artisan that the inventor had possession at that time of the . . . claimed subject matter.' "*Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 [ 19 USPQ2d 1111 ] (Fed. Cir. 1991) (quoting *Ralston Purina Co. v. Far - Mar-Co., Inc.*, 772 F.2d 1570, 1575 [ 227 USPQ 177 ] (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375 [ 217 USPQ 1089 ] (Fed. Cir. 1983))); *Fiers v. Revel*, 984 F.2d 1164, 1170 [ 25 USPQ2d 1601 ] (Fed. Cir. 1993) (citation omitted). Whether a patent's specification contains a disclosure that satisfies 35 U.S.C. Section 112 Para. 1 is a question of law; compliance with the written description aspect of that requirement is a question of fact. *Utter v. Hiraga*, 845 F.2d 993, 998 [ 6 USPQ2d 1709 ] (Fed. Cir. 1988) (citations omitted).

In the instant case, Lilly contends that its position is supported by *Amgen, Inc. v. Chugai*

*Pharmaceutical Co., Ltd.*, 927 F.2d 1200 [ 18 USPQ2d 1016 ] (Fed. Cir. 1991), and *Fiers v. Revel* , 984 F.2d 1164 [ 25 USPQ2d 1601 ] (Fed. Cir. 1993). In *Amgen*, the Federal Circuit held that

when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated.

*Amgen*, 927 F.2d at 1206. Although *Amgen* dealt with the issue of conception, [FN25] its application to this case is clear. If an inventor has not achieved conception of an invention, he would be unable adequately to describe the invention in a fashion that satisfies 35 U.S.C. Section 112 Para. 1. In fact, the *Fiers* court stated:

. . . If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name, or physical properties, as we have held, then a description also requires that degree of specificity. To paraphrase the Board, one cannot describe what one has not conceived.

*Fiers*, 984 F.2d at 1171. Also in *Fiers*, the court explained that

[a]n adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself. . . . A bare reference to a DNA with a statement that it can be obtained by reverse transcript ion is not a description; it does not indicate that [the patent applicant] was in possession of the DNA.

*Fiers*, 984 F.2d at 1170-71.

Although *Amgen* and *Fiers* provide guidance for our decision today, yet they do not furnish us with a definitive answer. Unlike the inventors in *Fiers* and *Amgen*, the inventors on the '525 patent actually had isolated and characterized a cDNA gene for insulin -- i.e., rat insulin. We must decide whether the isolation and characterization of one species allows the inventor to claim the genera in which that species is a member, as well as other species from those genera. We think that it does not.

[5] In examples one through five of the '525 patent's specification, the inventors describe the extraction and isolation of rat insulin mRNA; the synthesis and characterization of double stranded cDNA containing the rat insulin sequence; the ligation of linkers to that double stranded cDNA; the formation of a recombinant plasmid and its characterization after replication; and further purification and sequence analysis. While prophetic example six suggests use of the procedures outlined in examples one through four within the context of human insulin, the specification provides no description of the "reverse transcript of an mRNA" for human insulin. The inventors could not provide a description of human insulin cDNA because they were not then in possession of that DNA. The '525 patent application has a file date of May 27, 1977, and the application was expanded on April 19, 1978, to add example six, relating to the potential isolation of human insulin DNA. However, it was not until nearly two years after the original application for the '525 was filed that UC inventors actually isolated and characterized human insulin cDNA.

***1241** At trial, Old opined that there are tens of thousands of members in the vertebrate genera. Tr. at 1390. The human, of course, is one species within that genera. Old testified that members of the vertebrate species do not have identical genes encoding insulin. *Id.* The human insulin cDNA, for example, differs from the rat insulin cDNA by four codons. [FN26] Tr. at 1841. Gilbert testified that it is impossible to use the rat insulin cDNA sequence to determine the human insulin cDNA sequence. Tr. at 1390. UC, itself, argued in the prosecution of the '740 patent that the differences in the nucleotide sequence were of major significance, and that such differences should render the human insulin cDNA patentable over the prior art -- prior art that included the '525 patent. UC Ex. 3 at A000160-61.

The PTO examiner disagreed; indeed, he already had permitted the inventors of the '525 patent to claim human insulin cDNA. We believe, however, that Federal Circuit cases decided after the examiner's consideration of the claims in issue reveal that the examiner erred when he determined that human insulin cDNA was patentable before it actually had been isolated and characterized. The Federal Circuit's holding that an adequate written

description of a DNA requires a "precise definition" leads us to conclude that the '525 patent's specification neither enables the patent's claims to all vertebrates and mammals, nor enables the claim targeting the human species. We are persuaded that the isolation and characterization of the proinsulin cDNA from one member of a genus is not sufficient to support claims to the insulin cDNA of thousands and thousands of other species from that genus. Consequently, we hold that the specification of the '525 patent adequately describes only the rat insulin cDNA; the inventors' claims to the genera of vertebrates and mammals and to the human species are invalid. [FN27]

B. *The '740 Patent -- Anticipation and Enablement* [FN28]

Preliminarily, we note that our earlier determination that claims five, six and eight through ten encompass only direct expression of human proinsulin distinguishes those claims from the prior art in issue, i.e., EPA-1929, such that EPA-1929 is not an anticipatory reference to the '740. Nevertheless, our previous interpretation of the claims in issue was based, in part, on our conclusion that the amino acid sequence for human proinsulin existed in the art before the file date of the '740 application. Moreover, UC steadfastly contends that the subject claims of the '740 patent encompass human proinsulin fusion proteins. Hence, we believe a discussion of the invalidity and enablement issues is necessary.

Lilly argues that EPA-1929 renders claims five, six and eight through ten of the '740 patent invalid under the doctrine of anticipation, pursuant to 35 U.S.C. Section 102(a). [FN29] UC counters that EPA-1929 cannot be an anticipatory reference because it does not meet the requirements for such. Specifically, a claim is anticipated only if all the elements and limitations of that claim are found within a single prior art reference. *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 [ 18 USPQ2d 1001 ] (Fed. Cir. 1991) (citing *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613, 619 [ 225 USPQ 634 ] (Fed. Cir.), *cert. dismissed*, 474 U.S. 976 (1985)). No ***1242** difference may exist between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of invention. *Id* . UC asserts that EPA-1929 did not include the amino acid sequence for human proinsulin, and that such exclusion requires use of a second reference -- a use that, according to UC, prevents the instant scenario from being considered under the doctrine of anticipation.

Lilly counters that in some instances extrinsic evidence is admissible to explain the disclosure of a reference. "This modest flexibility in the rule that anticipation requires every element of the claims to appear in a single reference accommodates situations where the common knowledge of technologists is not recorded in the reference; that is, where technological facts are known to those in the field of the invention, albeit not known to judges." *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269 [ 20 USPQ2d 1746 ] (Fed. Cir. 1991). The extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill."*Id.* at 1268.

Lilly contends that the amino acid sequence for human proinsulin was a sequence well known by those in the field of molecular biology. Consequently, Lilly posits, failure to include the sequence in EPA-1929 does not prevent that publication from anticipating certain claims of the '740 patent. Lilly also frames this issue in the context of enablement. Specifically, Lilly argues, claim six of EPA-1929 explicitly described the subject matter of the claims in issue; claim six of EPA-1929 was enabling; and, thus, EPA-1929 anticipated the subject claims of the '740 patent. [FN30]

Anticipation is a question of fact. *Scripps Clinic & Research Found.*, 927 F.2d at 1576. Enablement is a mixed question of law and fact, both in the context of whether a specification sufficiently enables a claim under 35 U.S.C. Section 112 and in the context of whether a prior art reference is enabling of the features for which it has been cited. *In re Epstein*, 32 F.3d 1559, 1568 [ 31 USPQ2d 1817 ] (Fed. Cir. 1994) (citing *In re Sasse*, 629 F.2d 675, 681 [ 207 USPQ 107 ] (C.C.P.A. 1980)). In order to conclude that EPA-1929 is enabling, the Court must determine that the amino acid sequence for human proinsulin, a sequence not disclosed in that prior work but essential to it, commonly was known by those skilled in the art -- that is, that the

prior art did not lack an enabling disclosure. *See In re Epstein*, 32 F.3d at 1568. This same determination is necessary in order for the Court to conclude that EPA-1929 is an anticipatory reference to the '740 patent because a reference cannot anticipate that which it does not enable. *See In re Paulsen*, 30 F.3d 1475, 1480 [ 31 USPQ2d 1671 ] (Fed. Cir. 1994) (holding that prior art sufficiently was enabling to serve as an anticipatory reference).

Our first determination in this arena requires that we assume the amino acid sequence for human proinsulin was known during the relevant time period. UC contends that, even under this assumption, anticipation is an improper legal theory for consideration of the present facts because, when practicing the invention of EPA-1929, those skilled in the art necessarily had to refer to a second source in order to ascertain the desired amino acid sequence. Fundamentally, UC argues that because those skilled in the art had not committed to memory the sequence for human proinsulin, Lilly's anticipation contention is misplaced.

> [6] We are unpersuaded that individuals skilled in the art must commit complex sequences to memory in order for those sequences to qualify as information within their common knowledge. We believe that once an amino acid sequence, such as that for proinsulin, finally is determined and widely is reported within the literature of the discipline, that sequence is within the experts' common knowledge, despite the fact that the experts have not memorized the formula. In the instant case, the sequence was reported not only in the *Atlas of Protein Sequence and Structure* ( *Atlas*), a reference book whose name is indicative of its contents, but also was reported in other literature in the discipline. [FN31]

Consequently, still operating under the assumption that the human proinsulin amino acid sequence reported was correct, the mere fact that an expert had to refer to a second source in order to obtain the specific sequence does not preclude an anticipation argument in the context of a prior art reference. We believe the modest flexibility in the rule governing anticipation is designed for just such situations. For our next analysis, ***1243** we remove the presumption we previously employed and consider if the correct amino acid sequence for human proinsulin actually was in the art prior to the time EPA- 1929 was published.

Four months passed between the publication date of EPA-1929 -- which is May 16, 1979 -- and the file date of the application for the '740 patent -- which is September 12, 1979. Lilly argues that the human proinsulin amino acid sequence was known before the earlier of the two dates; UC contends that the sequence was not known until the later date, at which time inventors of the '740 patent actually isolated and characterized the human source DNA that codes for proinsulin.

Human proinsulin consists of 86 amino acids and contains three distinct segments -- the B-chain, the C-peptide and the A-chain. The C-peptide is located between the B- and A-chains and serves to connect them. [FN32] During the process in which human proinsulin is converted into human insulin, the C-peptide is liberated at two cleavage sites, leaving only the A- and B-chains of human insulin.

The parties' disagreement about the human proinsulin amino acid sequence arises over the aforementioned cleavage sites (or dibasic amino acid residues). These cleavage sites are (1) the two amino acids that link the C-peptide to the B-chain of the proinsulin molecule; and (2) the two amino acids that link the C-peptide to the A-chain of that molecule. *See* UC Post-trial Br. at 37. Between the C-peptide and the B-chain, the amino acids are two arginines; between the C-peptide and the A-chain, the amino acids are one lysine and one arginine, in that order. Lilly contends that both the composition and order of these four residues were in the art at the time EPA-1929 was published. In contrast, UC argues that although the composition of those residues was known, yet the order in which they appeared in the proinsulin chain was not known. Consequently, we must determine the status of the knowledge regarding these dibasic amino acid residues in 1979. [FN33]

The human proinsulin amino acid sequence first was reported in a 1971 article entitled "Studies on Human Proinsulin: Isolation and Amino Acid Sequence of the Human Pancreatic C-Peptide" (the Oyer *et al.* article), [FN34] based on a study in which scientists examined the C-peptide region of human proinsulin. UC Ex. 43. The sequence identified in the Oyer *et al.* article later was catalogued in the *Atlas*, appearing in the 1972 *Atlas*

and in its 1976 and 1978 supplements.

UC contends that although these publications reported the correct amino acid sequence for human proinsulin, yet the sequences were not reported with certainty. For example, UC focuses on the Oyer *et al.* article and the authors' use of such phrases as " *proposed* partial amino acid sequence of human proinsulin" and "the *probable* locations of the four additional basic residues present in human proinsulin." Lilly Ex. 3118 at 1384. Moreover, UC asserts that recitation of the proinsulin amino acid sequence in the *Atlas* and its supplements provides no more certainty than the Oyer *et al.* article. Specifically, UC notes that the dibasic residues are enclosed in special punctuation indicating that those residues only have been determined with 90 percent confidence.

> [7] In large part, the qualifying statements accompanying the published human proinsulin amino acid sequence persuaded this Court to deny Lilly's earlier motion for partial summary judgment that claims five and six of the '740 patent are invalid under the doctrine of anticipation. We now are convinced, however, in light of the additional evidence presented at trial, that these qualifying statements do not illustrate that the amino acid sequence for human proinsulin commonly was not known by those skilled in the art by early 1979. To the contrary, we find that it was known at least as early as 1971.

We begin our analysis with a survey of the literature and the results of research in existence prior to May of 1979. Lilly expert Dr. Donald Steiner (Steiner) testified that during the 1968 time frame, he and co-workers determined that the dibasic amino acid residues in bovine (cow) proinsulin linking the B-chain and the C-peptide were two arginines and that the dibasic amino acid residues linking the C-peptide and the A-chain were one arginine and one lysine. Tr. at 1497-99. Steiner also averred that during the same time period, Dr. Ronald Chance (Chance), a Lilly researcher, was investigating the porcine (pig) proinsulin structure. Tr. at 1497-1498. Steiner stated that Chance established that the dibasic amino acid residues ***1244** in porcine were the same as those in bovine. Tr. at 1501-02.

The identity in structure of the dibasic amino acid residues in these two mammals was no surprise to scientists, according to Steiner. Specifically, Steiner explained that these residues have a very significant function in nature -- that of providing a cleavage site for enzyme removal of the residues and the connecting C-peptide from the A- and B-chains of insulin. Tr. at 1503- 05. Because these residues play a vital role in the conversion of proinsulin to insulin, Steiner stated, its structure is highly conserved "in proinsulins across the mammalian species for sure, and probably in even much more primitive species as well." Tr. at 1503-05.

Gilbert further described the high conservation of the dibasic amino acid residues in proinsulin across the mammalian species. Gilbert first noted that the evolutionary analysis involved in the discussion of conservation of residues was in existence during the relevant time period in this case. Tr. at 1412. When asked why one would expect to find the same amino acids in the dibasic residues of all mammals, Gilbert responded:

> Because [that] part of the molecule has an essential function; and therefore, a mutation which changes the amino acid tends to inactivate the molecule. Part of the molecule that doesn't have an essential function, which is sort of waving in the wind over here, when you change that amino acid, it doesn't matter. But if I've got to do something very special with that piece of the molecule and I try to change it, then I'm in trouble.

Tr. at 1414. *See also* tr. at 708 (wherein Richards, UC's expert, testified that the dibasic residues have a critical function in human proinsulin).

Gilbert explained that the evidence available before 1977 indicated that the ancestral protein for proinsulin had dibasic residues consisting of (1) two arginines between the B-chain and the C-peptide, and (2) a lysine and an arginine between the C-peptide and the A-chain. Gilbert testified that up to 1977, one might have argued that a mutation could have occurred, resulting in the human residues differing from those in the ancestral protein. Gilbert first opined that such mutation would have been extremely unlikely. Tr. at 1414-15. Second, he stated that evidence becoming available in 1977 and 1978 further strengthened the finding that the dibasic amino acid residues were highly conserved among mammals. Two

experiments in the rat, another mammalian species, concluded that the residues were the same as they were for the cow and pig -- (1) two arginines and (2) one lysine and one arginine. *See, e.g.*, Lilly Ex. 3761. Gilbert focused on the rat experiment conducted by UC scientists in his testimony. [FN35]

Gilbert explained that this rat experiment revealed information concerning the make- up of the actual ancestral codons. [FN36] Tr. at 1416. According to Gilbert, this revelation was significant. Specifically, there are two sets of bases that encode the amino acid lysine; and there are six sets of bases that encode the amino acid arginine. *See* Lilly Ex. 3766. Some of the sets of bases that encode arginine would require fewer base mutations than other codons in order to change the arginine into a lysine. [FN37] Tr. at 1417. In the rat experiments, it was determined that the codons encoding the arginine residues were from among those sets of bases requiring two or more mutations in order to change a arginine into a lysine, making it extremely unlikely that such change would have occurred. Tr. at 1418. Gilbert testified that the likelihood of a single mutation occurring is approximately a one percent chance in every million years. Tr. at 1417. He further stated that " [t]o get two changes is then essentially the product of two, one percent chances every million years. . . [I]t's much less likely." Tr. at 1417-18. Gilbert said that the rat experiment illustrated that it was "essentially impossible" that in the dibasic residues an arginine could have changed to a lysine or that a lysine could have changed to an arginine. [FN38] Tr. at 1418.

[A]nybody who knew enough molecular biology to discuss sequences [at the time period in issue] and knew enough evolution to read the Dayhoff *Atlas* would have been quite sure that the sequence was correct as given for the . . . dibasic amino acids.

***1245** Tr. at 1418-19.

The Court finds this evidence highly persuasive. The testimony indicates that by 1971, experts in the field had no reason to doubt not only the composition of the dibasic amino acid residues in human proinsulin, but also the order of those residues. Indeed, Steiner and Richards both testified that they were unaware of any publication subsequent to the 1971 Oyer *et al.* article proposing a different structure for human proinsulin. Tr. at 707, 1532. Moreover, Steiner averred that had he believed in 1971 any question existed concerning the order of the dibasic residues, he then could have sequenced these residues by a direct method. [FN39] Tr. at 1532-34. Steiner said that the supply of human proinsulin was very limited at the time and, thus, was used to identify those parts of the sequence that were not conserved. Tr. at 1533-34.

Other evidence suggests that even UC researchers, themselves, believed that the amino acid sequence for human proinsulin already existed in the art. The June 1977 *Science* article, [FN40] authored by UC's Ullrich, Shine, Chirgwin, Pictet, Edmund Tischer, Rutter and Goodman, provides one example. In that article, the researchers, *inter alia*, describe the nucleotide sequence of the cloned DNA of rat proinsulin. The authors stated:

Previous data did not provide assignments for the basic arginine or lysine residues connecting the B-C-A peptides, although they had been inferred by analogy with the bovine, porcine, and *human proinsulin* sequences.

UC Ex. 98 at 1316. This passage reflects that the UC researchers believed that the dibasic residues in human proinsulin had been determined. Apparently, they were certain enough about the order of those residues to use them as a point of reference for the consideration of the proinsulin sequence of another mammalian species -- the rat.

Additionally, the specification of the '740 patent itself indicates that UC researchers believed that the amino acid sequence for human proinsulin already existed in the art. In the background of the invention, the inventors state that " [t]he amino acid sequence for human proinsulin, determined by conventional techniques, is given in Table 1." UC Ex. 1 at col. 1. The inventors explain that in Table 1, the C-peptide is amino acids 31-65, meaning that their description of the C-peptide includes the dibasic amino acid residues flanking each end of the C-peptide. [FN41] Table 1 lists these residues as arginine-arginine and lysine-arginine. *Id.* When co-inventor Bell was questioned at trial, the following colloquy ensued:

Q. Isn't it true that in your deposition when you were confronted with the text of your patent application, stating that the amino acid sequence

determined by conventional techniques was described in figure 1 of your application, you stated, "I suspect we overlooked those details about the basic amino acids." Is that right?

A. You know, I can't tell you what I think at the time I read this paper. Obviously we had determined the sequence of human insulin cDNA and we wanted to have this information in print as rapidly as possible. It was being submitted as a letter to Nature where there's a limitation on words. And so we didn't include things that perhaps we should have or could have.

Q. I'd like to hand you a copy of your deposition transcript and ask you to turn to page 70. Starting at line 18, my question will be did you give the following answers to the following questions:

"Question: Would you read the text of your application in column 1 starting at line, it looks like about 487, do you see there where it says the amino acid sequence for human proinsulin determined by conventional techniques is given in table 1; do you see that?

"Answer: Yes.

[Question:] "Do you have any reason to believe it was untrue when you signed it in 1979?

"Answer: I suspect we overlooked those details about the basic amino acids."

***1246** Did you give that testimony, Dr. Bell?

A. I signed this, didn't I?

Tr. at 1100-01.

Moreover, in example one of the specification, the inventors assert:

The primary structure of human proinsulin determined in this manner [that is, determined by nucleotide sequencing] agrees precisely with that obtained by previous amino acid sequencing experiments. (Dayhoff, M.D., Atlas of Protein Sequence and Structure, 5, Supp. 2, pp. 127-130 (1976) and Suppl. 3, pp. 150- 151 (1978).

UC Ex. 1 at col. 12. This language does not support UC's assertion that its inventors were claiming as a part of their invention the characterization of the amino acid sequence for human proinsulin. Rather, the inventors appear only to reaffirm that which already was reported in the literature. In light of not only the specification's lack of assertion of discovery concerning the amino acid sequence of human proinsulin, but also its language directly contradicting UC's current contention of discovery, we are clearly convinced that even UC believed that the amino acid sequence was in the art as early as 1977.

Finally, communications between UC representatives after the '740 patent issued further convince the Court that the '740 patent inventors did not consider themselves the discoverers of the amino acid sequence for human proinsulin in 1979 when they submitted the application for the '740 patent to the PTO. In October of 1985, a Lilly representative conveyed to a UC representative certain scope and validity concerns regarding claim five of the '740 patent in light of the published amino acid sequence of human proinsulin. *See* Lilly Ex. 3501.

On November 5, 1985, Marilyn Ziemer (Ziemer), UC's licensing associate, received a letter from Dr. Kate Murashige (Murashige), UC's outside patent counsel at that time. In this letter, Murashige questioned Ziemer about whether the amino acid sequences for human preproinsulin and proinsulin were known before the application for the '740 patent. UC Ex. 328. Ziemer received Murashige's letter on November 8, 1985. On that same day, Ziemer called Rutter, one of the four inventors named on the '740 patent. Although at her deposition on April 22, 1994, Ziemer [FN42] then could not recall her conversation with Rutter, yet she confirmed that a November 8, 1985, memorandum to the file was a document authored by her in which she recorded the subject conversation. Ziemer read what she had written in her memorandum to the file:

A. "Sequence of Proinsulin C-peptide [FN43] was known at the time of cloning. Only the pre sequence was not known."

. . .

A. "I noted the 'Catch 22' type problem that the claims as issued may be construed to cover only the

natural cDNA sequence and no variations even though they cover the same resultant protein. Rutter suggest we might argue that other sequences (besides the cDNA) are functionally equivalent.

"Maybe we should consider reissuing. We only have until February '86. Rutter believes it is not practical (maybe even impossible) to make a sequence of the proinsulin size synthetically. Thus claim five may not be obvious for only that reason."

Ziemer Hartig Dep. at 181-83 (April 22, 1994).

Later, UC's concerns regarding the '740 patent were crystallized in a July 26, 1986, opinion letter to Ziemer authored by Murashige.

It appears that the issues raised by Lilly were never raised in the prosecution. It was never proposed that the generic sequence as claimed in claims 4 and 5 was made obvious by *Crea* in combination with known amino acid sequences. Nor was the claimed generic sequence ever asserted to have been made obvious simply by disclosure of the amino acid sequence of proinsulin, *which by applicants own admission*, already existed in the art.

. . .
Lilly Ex. 3509 at 0009242-43 (emphasis added).

Finally, in a May 26, 1987, letter from Murashige to Valentin Fikovsky, manager of patent prosecution at the University's patent, trademark and copyright office, Murashige wrote:

. . .
The posture with regard to insulin, then, is that there is no prior publication describing the cloning of cDNA, although, *certainly*, the amino acid sequences for the A and B chains and *for proinsulin were known*, and certainly the existence and ***1247** probably the amino acid sequence for preproinsulin also was known.

. . .
Lilly Ex. 3280 at H1495 0491 (emphasis added).

These communications convince the Court clearly that even UC recognized and accepted that the amino acid sequence for proinsulin already was in the art before the date of the application for the '740 patent. Indeed, we believe that the PTO examiner's mandated amendment in claim five was a direct result of his recognition that both fusion proteins and the amino acid sequence for human proinsulin already were in the art.

UC argues that Lilly, itself, has stated that the subject sequence was not known during the relevant time period. For this contention, UC relies on statements Lilly made to the Food and Drug Administration (FDA) in a new drug application (NDA) for PRO-Humulin. Specifically, UC argues that in the following excerpt Lilly admits UC inventors are they who determined the correct amino acid sequence:

The amino acid sequence of human proinsulin was deduced by Steiner, *et al* to be as shown in Figure 1. This structure was based on separate determinations of the sequence of human insulin and human C-peptide. Only small quantities [ ] of human proinsulin have ever been isolated from human pancreas. . . .The final confirmation of human proinsulin amino acid sequence has come from sequencing of the DNA that codes for human proinsulin. Because of the very limited quantities of pancreatic human proinsulin that have ever been isolated, this material is not available for use as a reference standard in the chemical and physical characterization of biosynthetic human proinsulin.

UC Ex. 68 at 118 (emphasis added).

We are unconvinced that this statement is an admission by Lilly that the amino acid sequence was unknown. Preliminarily, we note that the standard for drug approval is different from the standard for patentability. *See, e.g., Application of Watson*, 517 F.2d 465, 476 [ 186 USPQ 11 ] (C.C.P.A. 1975) (holding that "Congress has given the responsibility to the FDA, not the Patent Office, to determine in the first instance whether drugs are sufficiently safe for use that they can be introduced in the commercial market. . . ."). Thus, it would appear that statements made in one context directly are not applicable in the other context. More importantly, from the aforequoted excerpt, we glean no Lilly admission. To the contrary, Lilly, by using the phrase "final confirmation," indicates that the subject sequence previously had been confirmed by others. Indeed, expert testimony from Steiner is in accord with this position.

Steiner reasoned that the authors' use of the term "proposed" when identifying the human proinsulin amino acid sequence in the Oyer *et al.* article merely was a "fairly conservative" way of stating their conclusion. Tr. at 1512. "It certainly simply means that we believed and concluded that would be the structure of human proinsulin as we were showing it there."*Id.* Regarding the dibasic amino acid residues, Steiner testified that the authors of the article "were completely confident" that the residues were ordered in human proinsulin as the article indicated -- two arginines between the B-chain and C- peptide and one lysine and one arginine between the C-peptide and A-chain. Tr. at 1513.

In view of the evidence of record, we are convinced clearly that the amino acid sequence for human proinsulin was known to those skilled in the art as early as 1971 and surely before 1978. Again, we believe that the PTO examiner recognized this when he limited claim five to direct expression. Moreover, even if the '740 patent were not limited to direct expression, Lilly's anticipation defense would have succeeded in invalidating the broad claims of the patent -- claims five, six and eight through ten. Because we find that the amino acid sequence for human proinsulin was in the art before 1978, claim six of EPA-1929 was enabling for human proinsulin.

III. *Inequitable Conduct*

In the prosecution of patent applications before the PTO, patent applicants have a duty of candor, good faith and honesty. *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178 [ 33 USPQ2d 1823 ] (Fed. Cir. 1995) (citing *Precision Instrument Mfg. Co. v. Automotive Maintenance Mach. Co.*, 324 U.S. 806, 818 [ 65 USPQ 133 ] (1945)); *see also* 37 C.F.R. Section 1.56 (1977). The applicant's representatives are bound by the same duty. *Id.* (citing *FMC Corp. v. Manitowoc Co.*, 835 F.2d 1411, 1415 n.8 [ 5 USPQ2d 1112 ] (Fed. Cir. 1987)). "A breach of this duty constitutes inequitable conduct."*Molins PLC*, 48 F.3d at 1178.

Conduct before the PTO that may render a patent unenforceable "includes failure to disclose material information, or submission of false material information, with an intent to mislead."*J.P. Stevens & Co., Inc. v. Lex Tex Ltd., Inc.*, 747 F.2d 1553, 1559 [ 223 USPQ 1089 ] (Fed. Cir. 1984), *cert. denied*, 474 U.S. 822 (1985).

***1248** One challenging a patent as unenforceable based on inequitable conduct must prove by clear and convincing evidence that the patentee either intentionally failed to disclose material information or intentionally submitted false material information to the PTO during the procurement of the subject patent. *Id.* Information is material if "there is a substantial likelihood that a reasonable examiner would have considered the information important in deciding whether to allow the application to issue as a patent." *mOlins pLC*, 48 F.3D at 1179 (citing *iN re jErabek*, 789 f.2D 886, 890 [ 229 USPQ 530 ] (Fed. Cir. 1986)). Moreover, " ' [t]o be guilty of inequitable conduct, one must have intended to act inequitably,' "*Kingsdown Medical Consultants v. Hollister Inc.*, 863 F.2d 867, 872 [ 9 USPQ2d 1384 ] (Fed. Cir. 1988) (quoting *FMC Corp. v. Manitowoc Co., Inc.*, 835 F.2d 1411, 1415 [ 5 USPQ2d 1112 ] (Fed. Cir. 1987)). The Federal Circuit has recognized that " [d]irect proof of wrongful intent is rarely available but may be inferred from clear and convincing evidence of the surrounding circumstances." *lAbOunty mFg., iNc. v. UNited sTates iNt'l tRade cOmm'n*, 958 f.2D 1066, 1076 [ 22 USPQ2d 1025 ] (Fed. Cir. 1992) (citations omitted).

A court cannot find inequitable conduct unless a threshold level of both materiality and intent to mislead are found. *Halliburton Co. v. Schlumberger Tech. Corp.*, 925 F.2d 1435, 1439 [ 17 USPQ2d 1834 ] (Fed. Cir. 1991) (citing *J.P. Stevens & Co. v. Lex Tex Ltd., Inc.*, 747 F.2d 1553, 1559-60 [ 223 USPQ 1089 ] (Fed. Cir 1984), *cert. denied*, 474 U.S. 822 (1985)). If these threshold levels are satisfied, the reviewing court then must balance the two elements to determine if the patent applicant has acted inequitably. *J.P. Stevens & Co.*, 747 F.2d at 1560.

In the instant case, Lilly contends that UC acted inequitably in the procurement of both the '525 patent and the '740 patent and, thus Lilly argues, both patents are unenforceable. We turn first to address inequitable conduct in the context of the '525 patent.

A. *The '525 Patent*

Some background information concerning research

involving recombinant DNA must precede discussion of this issue. In the early 1970's -- when experiments in the area of recombinant DNA were first contemplated -- many people, including some scientists, were concerned that such experiments might pose medical threats to humans. Tr. at 1295. The National Academy of Sciences eventually "called for a broad moratorium on all recombinant experiments until they could be . . . better reviewed by the scientific community."*Id.* At a subsequent review of recombinant DNA research in 1975, it was suggested that experiments in that area might proceed if suitable guidelines were promulgated to govern the research. *See* Lilly Ex. 3547 at HG2 580773.

Consequently, the Recombinant DNA Molecule Program Advisory Committee, previously established by the Department of Health, Education, and Welfare's National Institutes of Health (NIH), held its first meeting to develop safety guidelines. *Id* . Those guidelines were issued by the NIH on June 23, 1976, and published in the Federal Register on July 7, 1976. Tr. at 1296, 1298; Lilly Ex. 3731 at 000004; Lilly Ex. 3547. "The NIH Guidelines establish [ed] carefully controlled conditions for the conduct of experiments involving the production of [recombinant DNA] molecules and their insertion into organisms such as bacteria." Lilly Ex. 3547 at HG2 580773. For example, the regulations classified types of biological containments (i.e., plasmids) and specified which ones could be used in certain recombinant DNA experiments. The regulations also governed the type of physical containment facilities (i.e., laboratories) in which scientists could conduct particular types of experiments. [FN44] The safety guidelines mandated that no plasmid could be considered to fall within an approved classification until it had been certified by the NIH Recombinant DNA Advisory Committee. Tr. at 1301.

The guidelines also stipulated that any institution receiving NIH funds was to appoint a principal investigator. [FN45] Under the guidelines, the principal investigator had certain responsibilities, including "supervising ***1249** the safety performance of the staff to ensure that the required safety practices and techniques [were] employed" and "investigating and reporting in writing to the NIH Office of Recombinant DNA Activities and the institutional biohazards committee (or biosafety committee) [FN46] any problems pertaining to operation and implementation of biological and physical containment safety practices and procedures, or equipment or facility failure." Lilly Ex. 3547 at HG2 580791. The guidelines governed the conduct of all NIH- supported research in the area of recombinant DNA. The research UC was conducting on rat insulin -- the research that formed the basis of the '525 patent -- was NIH-supported. Consequently, UC was to operate within the strictures of the safety guidelines.

By January of 1977, the NIH only had certified the plasmids denominated pSC101 and pCR1 for experiments with mammalian DNA. Tr. at 1301. According to Rutter, UC scientists delayed their recombinant DNA research, awaiting the NIH green light on use of a more advanced vector -- either pMB9 or pBR322. Tr. at 127. Rutter said UC representatives preferred to use pBR322. *Id.* Reportedly, that vector would be the most effective cloning agent. *Id.* On April 18, 1977, the NIH certified plasmid pMB9 as safe. Lilly Ex. 3554A at 177. On July 7, 1977, the NIH certified plasmid pBR322. *Id.*

Lilly contends that UC researchers knowingly used a plasmid not yet certified for use -- PBR322 -- in conducting its rat insulin experiments. Moreover, Lilly argues that UC researchers misrepresented the origins of their rat insulin data to the public, the NIH, the United States Senate [FN47] and the PTO in order to conceal their misuse of plasmid pBR322. According to Lilly, the UC researchers' misuse of the plasmid and misrepresentations of the origins of their data are material to patentability of the '525 patent, and the misrepresentations of their data were intended to mislead the PTO. Thus, Lilly argues, a finding of unenforceability based on inequitable conduct is appropriate.

Clearly, UC's scientists used pBR322 in their research before the NIH had certified that plasmid for use. In January of 1977, working in Goodman's laboratory at the University, Ullrich began using pBR322 in his recombinant DNA experiments. Ullrich testified that he began using the plasmid after a colleague informed him by telephone that the NIH had approved pBR322 for use. Tr. at 797-98; Lilly Ex. 3420 at HG 002878. The record indicates that prior to his use of pBR322, Ullrich informed Rutter

that he had heard pBR322 was approved and that he intended to proceed with his experiments. Dr. Rutter concurred with Dr. Ullrich's plan, without further verification of the status of pBR322.

Lilly Ex. 3420 at HG 002870.

Subsequently, during a February 4, 1977, meeting, certain UC researchers -- including Ullrich and Shine -- learned that although approval of pBR322 had been recommended, the NIH director's requisite certification of the plasmid as safe had not yet issued. [FN48] Lilly Ex. 3420 at HG 002871-72. Ullrich averred that he earlier had not been aware of the distinction between approval and certification. Tr. at 800. Thus, UC's premature use of pBR322 through February 4, 1977, was a violation of the NIH guidelines, but it was not necessarily an intentional violation.

The record, however, illustrates that UC researchers did not halt their use of pBR322 and/or the fruits of previous experiments with that vector after learning that pBR322 had not been certified. In fact, UC agrees that the experiments continued until at least March 3, 1977. Lilly Ex. 3420 at HG 002871. In its report to the Office of Recombinant DNA Activities (ORDA) concerning ***1250** UC's premature use of pBR322, [FN49] UC's biosafety committee stated:

At this [February 4] gathering, the investigators in Dr. Goodman's laboratory (including Drs. Ullrich and Shine) reportedly learned for the first time that there was some confusion about the status of pBR322 . . . However, the initial cloning experiments with pBR322 and insulin cDNA had been completed, and clones had been obtained. After February 4, no new clones were constructed, but those already obtained were grown up and examined for the presence of recombinant DNA.

. . .

There is no satisfactory explanation as to why the investigators in Dr. Goodman's laboratory continued experiments with these recombinant plasmids after February 4.

Lilly Ex. 3420 at HG 002872. Moreover, when questioned at trial, Ullrich did not deny use of pBR322 after learning that it had not been certified. Tr. at 824. We find that the record clearly supports Lilly's contention that UC knowingly violated NIH safety guidelines when its researchers continued to use pBR322 in recombinant DNA experiments even after learning that the plasmid had not yet been certified for use.

Additionally, neither Rutter nor Goodman officially reported the unauthorized use of pBR322 to the NIH after the time they became aware of the prohibited use. Rather, Rutter testified that he had an informal telephone conversation with Dr. DeWitt Stetten (Stetten), NIH deputy director for science, and that he and Stetten ultimately decided against a formal disclosure of the incident. Tr. at 129-30. In fact, Rutter testified that the conversation between Stetten and himself "was carried out in a deliberate way to convey the fact, but not to create a need to disclose . . . [t]o make a formal disclosure . . . There was no formal disclosure." Tr. at 246. Rutter also testified that during the conversation, Stetten and Rutter decided that the pBR322 clones would be destroyed. *Id.* at 131. This conversation reportedly occurred sometime between March 16-19, 1977. Lilly Ex. 3420 at HG 002873.

Furthermore, neither Rutter nor Goodman informed UC's own biosafety committee of the misuse of pBR322. Rather, Dr. David Martin (Martin), then chairman of UC's biosafety committee, "heard rumors" of the incident through a technician in Rutter's lab sometime in May, 1977. Tr. at 227; Lilly Ex. 3420 at HG 002874. Martin then discussed the matter with Rutter and Goodman. *Id.* At a June 3, 1977, biosafety committee meeting, Martin reported the UC scientists' use of pBR322. However, an examination of the minutes of that meeting indicates that the committee was not informed fully of the events that had occurred. As UC stated in its committee report to the NIH,

[t]he failure of the Biosafety Committee to notify the NIH of the pBR322 incident was primarily a consequence of the fact that the Committee itself was unaware of the details and import of the event. On the basis of the information the Committee had at that time, it was not aware that a violation had occurred.

Lilly Ex. 3420 at HG 002874.

Thus, it is obvious that UC representatives did not formally report UC's researchers' violation of the

guidelines to the NIH, nor did they provide a detailed explanation of the incident to UC's biosafety committee at its June 3, 1977, meeting. Events occurring later, however, brought the incident to the surface.

On September 9, 1977, Nicholas Wade (Wade), a *Science* reporter, called Dr. William Gartland (Gartland), director of ORDA, asking questions about UC's alleged use of an uncertified plasmid. Lilly Ex. 3731 at 000095. Wade stated that he was writing an article about the pBR322 incident -- an article that subsequently was published in the September 30, 1977, issue of the publication. *Id.* at 83, 87. Gartland apparently first learned of UC's inappropriate use of the plasmid during Wade's telephone call to him. *Id.* at 83.

On October 11, 1977, Gartland wrote Dr. James Cleaver (Cleaver), chairman of UC's biosafety committee, asking for an accounting of the incident. Lilly Ex. 3731 at 000088-89. Cleaver responded on October 25, 1977, including in his response a memorandum authored by Goodman and Rutter detailing, as they recollected, the events surrounding the pBR322 incident. Lilly Ex. 3731 at 000090, 000092. In the memorandum, Goodman and Rutter stated that the decision was made to destroy the pBR322 clones. No date was affixed to this decision. *Id.* However, in the biosafety committee's January 20, 1978, report to the NIH -- in which the committee answered NIH questions about UC's misuse of pBR322 -- Rutter and Goodman said that Ullrich, the UC scientist actually working with the plasmid, told them that he disposed of the pBR322 ***1251** clones on March 19, 1977. [FN50] Lilly Ex. 3420 at HG 002873.

It is clear from the record that Ullrich did not destroy all the material associated with pBR322. He saved the purified DNA associated with the use of pBR322 plasmids, and Goodman and Rutter were aware that he did. In registered letters that Rutter and Goodman testified to having exchanged during the events in issue, they admitted that they chose to " [k]eep the cloned DNA since the experiments had already been performed . . . We believed that further sequencing of the DNA clones was acceptable since the hypothetical danger, if any, is not with the DNA itself." Lilly Ex. 3361 at HG 000691-92; Lilly Ex. 3363 at WR 10720-21; *see also* tr. at 231-234, 1149-1153. Goodman's letter to Rutter was sent March 25, 1977; Rutter's letter to Goodman was sent March 22, 1977. These "smoking gun" letters could have had no purpose but to keep either of the writers from attributing the misuse to the other.

At trial, Rutter and Goodman testified that although the letters reflect that they chose to retain the cloned DNAs, they actually chose a different course of action. They contended that they destroyed all the cloned DNAs. Tr. at 302, 1111. When asked why he and Goodman did not amend their letters to reflect a different decision, Rutter responded:

Because actually we acted on the advice of DeWitt Stetten and destroyed the clones. It was unnecessary to adapt this guideline. We had carried out the activities which we had decided, namely, to destroy the clones for pBR322.

Tr. at 302.

We believe the registered letters are reflective of Rutter and Goodman's contemporaneous level of concern over the pBR322 incident. We are far from convinced that the two would go so far as to mail identical registered letters to one another admitting to having taken a course of action that flew in the face of NIH regulations and, subsequently, upon abandoning that course of action, permit those letters to stand uncorrected in their respective files. Moreover, the earlier of these registered letters was dated March 22, 1977. Rutter's telephone conversation with Stetten was, at the latest, on March 19, 1977. Thus, the letters were exchanged *after* Rutter and Goodman had time to contemplate and decide their course of action and *after* the time Ullrich allegedly destroyed the tainted materials. In light of the persuasive nature of the registered letters and other evidence of record, we find Rutter and Goodman's trial testimony regarding the letters not credible.

In addition, Ullrich's trial testimony indicates that Goodman and Rutter did not decide to abandon use of the pBR322 DNA clones after they learned of pBR322's uncertified status. After Ullrich's recollection was refreshed by an examination of one of the registered letters, the following dialogue transpired:

Q. Does that refresh your recollection that you were, in fact, instructed by Drs. Goodman and Rutter to continue to work with the DNA even after you learned it was not certified?

A. I wouldn't use the word "instructed."

Q. Would you turn to Defendant's Exhibit--

THE COURT: Wait just a minute. What word would you use?

THE WITNESS: It was probably the result of a discussion and an agreement among more than Drs. Howard Goodman and Rutter.

Tr. at 829.

We find by clear and convincing evidence that UC representatives continued to use at least the fruits of the uncertified plasmid in sequencing experiments well beyond the time they learned that such use was inappropriate. The Court believes such use is tantamount to use of the plasmid itself. Next, we must determine whether UC researchers misrepresented the origins of the rat insulin data -- data on which the '525 patent is based.

On May 9, 1977, Rutter submitted to the journal *Science* a manuscript in which UC researchers described the isolation of four pieces of rat insulin DNA. Lilly Ex. 3391; Lilly Ex. 3380. The pieces of DNA isolated and sequenced were denominated in the *Science* article as pAU1, pAU2, pAU3 and pAU4. The researchers stated in their manuscript describing their rat insulin work that they had used the bacterial plasmid pMB9 in their research efforts. Notably, pMB9 was not certified for use by the NIH until April 18, 1977.

Lilly contends that although UC researchers asserted that the work leading to the *Science* manuscript -- and, ultimately the '525 patent -- was done with plasmid pMB9, yet actually the work was done with the uncertified vector pBR322. Lilly argues that ***1252** the DNA pieces described in the *Science* article really are those DNA clones obtained by UC's unauthorized use of pBR322. An examination of the evidence and trial testimony leads us to conclude that Lilly's position is well supported. We explain.

Ullrich maintained a laboratory notebook regarding his research activities and in that notebook he described his work with pBR322. *See* Lilly Ex. 3340. In his notebook, Ullrich specified which of the DNA clones showed a positive result from a hybridization experiment involving microorganisms transformed by the uncertified pBR322 plasmids containing rat islet cDNA. *Id.* at HG 000445; tr. at 834-37. Ullrich labelled each of the clones for identification purposes. Tr. at 835-37. Significant to this discussion are the clones he labelled 1-13, 3-9 and 3-10.

Reference to these same clone numbers, i.e., 1-13, 3-9 and 3-10, was found on certain pages contained in a folder designated "INSULIN expt" from Howard Goodman's files. *See* Lilly Ex. 3354 at HG 002075. Ullrich admitted that the numbers 1-13, 3-9 and 3-10 "match with the numbers that we had seen before on the hybridization experiment." Ullrich further testified that several of the pages found in this folder contained his handwriting. Tr. at 840-41. He also agreed that the page in this folder entitled "Summary of Insulin Clones" includes a diagram that describes where the pieces of DNA from pBR322 started and stopped. Tr. at 841.

At trial, Gilbert, in his expert testimony, relied on Ullrich's lab notes, the insulin experiment folder from Goodman's files, and a handwritten manuscript draft describing an experiment conducted in the plasmid pBR322. [FN51] *See* Lilly Ex. 3365. Gilbert compared the sequence data from the unauthorized pBR322 research work with the sequence data reported in the *Science* article and concluded that the pieces of DNA reported in the article were derived from pBR322 research. Tr. at 1308, 1310-33. He stated that clone pAU-1 listed in the *Science* article contained the same starting and stopping points as pBR322 clone 1-13; pAU-2, the same as pBR322 clone 3-9; and pAU-3, the same as pBR322 clone 3-10. *Id.* Moreover, Gilbert testified that pAU-4 identified in the *Science* article corresponds to other sequence data reported in the pBR322 research. Tr. at 1321-22.

Gilbert was asked whether a second experiment, conducted in the same way as that with pBR322, likely would result in the isolation of clones having the same structure. Tr. at 1332. Gilbert answered that a researcher might isolate another clone having the same structure as that identified as 3-9. Tr. at

1333- 34. However, he added that the same was not true of clones 1-13, 3-10 or that identified as pAU-4 in the *Science* paper. *Id.* In these fragments, one would have expected variations in other experiments. *Id.* Even Ullrich declared it highly unlikely that the sequence reported in pAU-4 would be duplicated by random chance. Tr. at 873-74. UC expert Richards concurred with Ullrich's observation. Tr. at 206.

The Court finds Gilbert eminently qualified and credible. Significantly, we find that the evidence supporting his interpretation of the sequence of events is clear and convincing. [FN52] Hence, we find that the duplications in the structure of pBR322-derived clones and the structure of clones reported in the *Science* manuscript and the original '525 patent application are not products of random ***1253** chance. Rather, we find that UC researchers used data derived from the pBR322 experiments in the aforementioned publications.

The Court also believes that comment on Rutter's testimony before the Senate subcommittee in November of 1977 is in order. After comparing the evidence of record against that testimony, we find that Rutter was not candid with members of the subcommittee. For example, Rutter testified that the experiments with the uncertified plasmid were not spurred by commercial interests. Lilly Ex. 3554A at 219. Rutter also averred that none of the work in the plasmid had any relationship to Genentech, Inc. (Genentech). [FN53]

Certain evidence of record counters Rutter's averments. The evidence indicates that UC representatives began collaboration discussions with both Genentech and Lilly shortly after learning that rat insulin DNA had been isolated in the uncertified pBR322. For example, on March 9, 1977 -- eight days after learning of UC's misuse of the plasmid and seven days after learning that an insulin clone actually had been obtained from pBR322 work -- Goodman contacted Lilly. Lilly Ex. 3400 at WR 10052. In his notes recording that conversation, Goodman wrote: "Have rat clone. Q. How? A. Don't want to say too much now, but can prove it." Lilly Ex. 3343A. Goodman met with Lilly personnel on March 14, 1977. Lilly Ex. 3349. In his notes of that meeting, [FN54] Goodman wrote that he discussed a plasmid but that when someone asked him what plasmid, he answered, "Can't say." *Id.* at HG 001462. Additionally, Goodman's notes reflect that he told those present that what he wanted in exchange for what he had to offer included "money for lab" and "consulting."*Id.* at HG 001465.

Other evidence indicates that Goodman also approached Genentech during the same time period. On March 12, 1977, he met with Genentech representatives; Goodman's handwritten notes of that meeting indicate that Genentech offered Goodman "money for salaries, supplies, equipment, shares (common) . . . [and] consulting for me." Lilly Ex. 3347 at HG 001355. The record illustrates that Goodman called Genentech representative Ron Swanson at home the following day. Lilly Ex. 3348 at HG 001357. Goodman's notes of that telephone conversation state that Goodman "[h]inted [at] we were bringing something very valuable to the co & should be compensated for -- difference in kind between 'idea' & 'having [it]."*Id.* at HG 001357. Subsequently, other handwritten notes by Goodman illustrate that on March 15, 1977, he again called Genentech and reported the following: "Problem that in Boyer plasmid. Lay low. Not approved. Can't apply for patent yet." [FN55] Lilly Ex. 3351 at HG 001364.

Significantly, although at trial Goodman could not recall when Rutter became involved in the Genentech negotiations, he did not dispute that Rutter did become involved. In fact, in Goodman's deposition of May 18, 1993, he testified that while Rutter was not present at the first of the Genentech negotiation meetings that he could recollect, Rutter was involved in all subsequent meetings. Tr. at 1237-38. Hence, contrary to Rutter's statements to the Senate subcommittee, we find that continued use of the fruits of the pBR322 research was driven by commercial interests and we find that those commercial interests were tied closely to Genentech. [FN56]

UC asserts that even if the Court determines that the sequence data in issue did stem from work done in the uncertified plasmid pBR322, Lilly still cannot succeed in its inequitable conduct charge. Specifically, UC argues that Lilly cannot prove by clear and convincing evidence not only that UC's act was material to the prosecution of the '525 patent , but also that UC representatives committed the act with an intent to deceive the PTO examiner.

In *General Electro Music Corp. v. Samick Music Corp.*, 19 F.3d 1405 [ 30 USPQ2d 1149 ] (Fed. Cir. 1994), the patent applicant, Samick, sought expedited examination of its ***1254** application because, Samick alleged, the claimed design was being infringed. *Id.* at 1406. In order to obtain expedited examination, Samick had to file a "petition to make special."*Id.*

At the time Samick filed its petition, the MPEP [Manual of Patent Examining Procedure] required that an applicant support a petition to make special with an oath or declaration alleging facts showing, among other things, "that he or she had made or caused to be made a careful and thorough search of the prior art or has a good knowledge of the pertinent prior art."

*Id.* (quoting MPEP Section 708.02, II(5)). In light of this requirement, Samick, through its attorney, submitted a declaration stating that a prior art search had been conducted.

However, a jury determined that, contrary to Samick's attorney's declaration, Samick had not conducted a prior art search and, thus, that Samick intentionally had made a material false statement to the PTO. *Id.* at 1407. The Court entered judgment against Samick based on inequitable conduct rendering its patent unenforceable. *Id.* at 1408. The Federal Circuit affirmed. *Id.*

> [8] We believe the decision in *Samick* illustrates that the Federal Circuit's application of the concept of inequitable conduct is not limited to situations in which the patent applicant intentionally misleads the PTO in the context of prior art. Rather, inequitable conduct may be found in a variety of circumstances in which the patent applicant has abandoned his duty of candor, good faith and honesty to the PTO.

We already have determined that certain of the data found in the '525 patent was the result of an experiment conducted in the uncertified pBR322 plasmid. Moreover, in its prosecution of the '525 patent, UC failed to report its use of that vector to the PTO examiner but rather reported use of pMB9 for the data in issue. In light of these findings, the Court must determine whether UC's misrepresentation to the PTO was material to the patentability of the '525 patent.

> [9] After considering the facts and the law, we find that there is a substantial likelihood that a reasonable examiner would have considered UC's unauthorized use of pBR322 important in his patentability determination. UC, as an institution that accepted funding from the NIH, was obligated to follow the guidelines issued by that agency; UC was aware of its obligation. Even after UC representatives admittedly learned of their premature use of the subject plasmid, they, nonetheless, continued, at the very least, to use the sequence data they secured from their tainted research. A reasonable examiner easily could have determined that without use of the unauthorized plasmid and the data therefrom, UC's application for the '525 patent would not have acquired its May 27, 1977, file date. Indeed, it is impossible to determine whether UC would have been the first to make patent application had its representatives followed the rules to which its competitors were bound.

The Court also must consider the issue of intent, though the issue need not detain us long. First, we consider UC's forbidden use of pBR322 long past its recognition of the uncertified status of that plasmid. Second, we reiterate our determination that UC representatives incorporated pBR322 data into the '525 patent application -- an incorporation that was not accompanied by candor or honesty in UC's prosecution of the '525 patent application. Considering the admissions contained in the exchange of letters between Rutter and Goodman, we find no room for doubt that UC's failure to reveal its unauthorized use of pBR322 was intentional. Moreover, the Court finds that such intentional failure necessarily was meant to deceive or mislead the PTO examiner. UC was aware of its violation of the NIH safety guidelines and apparently was concerned that the PTO would endorse neither its experimental use of uncertified pBR322 nor its use of the results of that experiment in the '525 patent application.

The United States Supreme Court has stated that

. . . a patent is an exception to the general rule against monopolies and to the right to access to a free and open market. The far-reaching social and economic consequences of a patent, therefore, give the public a paramount interest in seeing that patent monopolies spring from backgrounds free from

fraud or other inequitable conduct and that such monopolies are kept within their legitimate scope.

*Precision Instrument Mfg. Co. v. Automotive Maintenance Mach. Co.*, 324 U.S. 806, 816 [ 65 USPQ 133 ] (1945). We are persuaded that endorsement of UC's conduct by enforcing the '525 patent would counter the public's interest. Hence, we hold that the '525 patent is unenforceable based on UC's inequitable conduct. [FN57]

***1255** B. *The '740 Patent*

Lilly contends that UC failed to disclose material prior art during its prosecution of the '740 patent, intending to deceive the PTO examiner. Similar to its preceding argument, Lilly asserts that such failure counters UC's duty of candor, good faith and honesty to the PTO, rises to the level of inequitable conduct, and renders the '740 patent unenforceable. [FN58] UC argues that the allegedly withheld prior art reference was, at most, cumulative; that UC did not intend to deceive the PTO examiner; and, hence, that UC did not procure the '740 patent inequitably.

Lilly's inequitable conduct charge arises from UC's failure to cite to the PTO examiner a European patent application (EPA-1929), which was filed November 6, 1978 and published on May 16, 1979 -- prior to the September 12, 1979, file date of the '740 patent. The disclosure of EPA-1929 was based on the work of Dr. Keiichi Itakura (Itakura) and Dr. Arthur Riggs (Riggs) and was embodied in other references as well. For example, the Itakura and Riggs disclosure also was contained in United Sates Patent Application Serial Number 849,692, filed by Itakura and Riggs on November 8, 1977. This application was embellished in November of 1979, and finally issued on November 3, 1987, as United States Patent Number 4,704,362 (the '362 patent). [FN59]

First, we must determine if the disclosure of EPA-1929 was material and not merely cumulative in the prosecution of the '740 patent. In our discussion at pages 46 through 65 of this Opinion concerning the issues of anticipation and enablement, we held that EPA-1929 was highly material to the prosecution of the '740 patent. In fact, we determined that the disclosure in EPA-1929 and its claim to human proinsulin make it impossible for the claims in the ' 740 patent to be interpreted as broadly as UC has urged.

We are convinced that certain of UC's arguments for patentability of the '740 patent application were contradicted by EPA-1929. Specifically, UC contended that the prior art cited by the PTO examiner actually taught away from the claimed invention because it did not suggest use of DNA encoding human proinsulin. UC. Ex. 3 at A000156, A000160. In a March 31, 1981, rejection of the '740 application, the examiner reasoned that the claims to proinsulin- encoding DNA were unpatentable in view of several publications. *Id.* at A000142. Relevant to this discussion, the examiner cited an article authored by Crea *et al.*, outlining the work of Itakura and Riggs wherein the scientists describe construction of synthetic DNA for the A- and B-chains of human insulin in separate plasmids. *Id.* at A000142, A000145; Lilly Ex. 3100.

UC responded to the examiner's rejection, arguing that

Crea *et al* teaches an entirely different approach to the synthesis of human insulin. That approach is to prepare separate and distinct transfer vectors comprising segments coding for the A chain and for the B chain. . . . That approach teaches away from the cloning of a single deoxynucleotide sequence coding for proinsulin.

. . .
The claimed preproinsulin and proinsulin cDNAs have utility in entirely different processes for the synthesis of human insulin, using an approach not taught or suggested by Crea *et al.*, or any of the cited references. . . .

UC Ex. 3 at A000156, A000160.

[10] UC appears correct in its assertion that none of the cited references suggested the approach of the '740 patent application. However, it is the uncited EPA-1929 that presents the problem. We find that EPA-1929 describes the very approach UC denied existed in any of the cited prior art. Not only does EPA-1929 describe the application of DNA synthesis techniques to human proinsulin DNA in a single plasmid, but, as we earlier noted, it actually includes a claim to a plasmid containing human proinsulin made in this fashion.

*See* Lilly Ex. 3047. Consequently, we cannot find that EPA-1929 was merely a cumulative reference.

Neither do we believe that UC was unaware of EPA-1929's materiality to prosecution of the '740 patent application. First, UC was informed through a January 2, 1980, 61-page evaluation by the law firm of Irons and Sears (the Irons opinion) [FN60] that, in the ***1256** author's view, the disclosure of EPA-1929 rendered the claims of the '740 patent *prima facie* unpatentable. *See* Lilly Ex. 3476 at 23847.

Second, the materiality of EPA-1929 to the examination of the '740 patent application was made clear to UC in the prosecution of foreign counterparts to the '740. UC filed a European patent application on September 11, 1980, which application corresponded to the United States application for the '740 patent. Lilly Ex. 3087. Additionally, UC filed corresponding applications in various countries, including France, Israel, Australia and New Zealand. *See* Lilly Exs. 3079, 3092A, 3089B, 3093B.

Sometime shortly after January 21, 1981, Lorance Greenlee (Greenlee), a Keil & Witherspoon attorney who was prosecuting the '740 patent for UC, [FN61] received a copy of a search report pertaining to the European patent application that corresponded to the '740 application pending in the United States. [FN62] Lilly Ex. 3064. The report, issued by the European Patent Office (EPO), informed the reader of documents considered by the EPO to be relevant to the prosecution of the European counterpart of the '740 patent application. Lilly Ex. 3091. The European report categorized the documents reported according to their level of relevancy. The search report in issue listed several documents. Significantly, EPA-1929 was categorized as particularly relevant -- the category used in European search reports to earmark a document of highest relevancy. *Id.* The search report specifically indicated that claim six -- the claim directed at human proinsulin -- was among the claims in EPA-1929 that were highly relevant to the '740 patent application's foreign counterpart. *Id.* Moreover, EPA-1929 was deemed more relevant in this search report than two documents that not only surfaced in the same search report but also were cited by UC during prosecution of the '740 patent application. Lilly Exs. 3000, 3091; tr. at 970-74.

In addition, at trial Lilly illustrated the following sequence of events. In January of 1983, Keil & Witherspoon was informed that a New Zealand counterpart of EPA-1929 had been cited against the New Zealand counterpart of the '740 patent application. PX 488 at 16611-12, 16615-17; tr. at 438-39. In April of 1983, Keil & Witherspoon was advised that EPA-1929 had been cited as particularly relevant against the French version of the '740 patent. Lilly Ex. 3080; tr. at 440-41. In June of the same year, Keil Witherspoon was notified that the German counterpart of EPA-1929 had been cited against the Israeli version of the '740 patent application. Tr. at 441-42. In August of 1983, Keil & Witherspoon was advised that EPA-1929 had been cited against the Australian version of the '740 patent application. Tr. at 443-44. None of UC's foreign applications succeeded.

Significantly, the Manual of Patent Examining Procedure (MPEP) effective during UC's prosecution of the '740 patent application contained a section entitled "Prior Art Cited in Related Foreign Applications." That section read as follows:

Applicants and other individuals as set forth in Section 1.56, have a duty to bring to the attention of the Office any material prior art or other information cited or brought to their attention in any related foreign application.

Manual of Patent Examining Procedure, Section 2001.06(a) (Revised 4th ed. 1980). Despite this rule and the many repeated notifications that EPA-1929 was material, UC representatives continued to prosecute the '740 patent application without citing EPA-1929 to the PTO examiner. Greenlee testified on direct examination that he could not recall considering the relevancy of EPA-1929 in the prosecution of the '740 patent application. Tr. at 931. On cross examination, Greenlee averred that he could not recollect why he did not cite EPA-1929 to the examiner. Tr. at 983. In fact, a perusal of Greenlee's trial testimony indicates that Greenlee's present recollection regarding any one of the issues about which he was cross-examined was poor to put it charitably. *See* tr. at 933-1033.

Greenlee's inability to recollect relevant subject matter, however, does not lessen the impact of the

paper evidence clearly illustrating that Greenlee was aware of the text of EPA-1929 by late 1979. *See* Lilly Exs. 3449, 3450, 3452, 3453, 3458. Moreover, all information Greenlee had acquired from other patent experts at that time indicated that a high level of materiality linked EPA-1929 to the '740 patent application. Indeed, the plain language of EPA-1929 included a claim to human proinsulin. Lilly Ex. 3047 at ***1257** claim six. The Court thus finds that UC representatives were aware that EPA-1929 was highly material to the prosecution of the '740 patent application.

With this materiality analysis behind us, we must consider the issue of intent. Lilly contends that EPA-1929's high level of materiality compels an inference of intent to mislead.

No single factor or combination of factors can be said always to *require* an inference of intent to mislead; yet a patentee facing a high level of materiality and clear proof that it knew or should have known of that materiality, can expect to find it difficult to establish "subjective good faith" sufficient to prevent the drawing of an inference of intent to mislead. A mere denial of intent to mislead (which would defeat every effort to establish inequitable conduct) will not suffice in such circumstances.

*FMC Corp.*, 835 F.2d at 1416.

We find that the facts of this case direct that we draw an inference of intent to mislead. First, we reiterate EPA-1929's high level of materiality. Indeed, under UC's proposed interpretation of the claims in issue, EPA-1929 was "but for" material. Even under the Court's interpretation of the claims -- an interpretation that limits the claims to plasmids coding for direct expression -- there is more than a substantial likelihood that a reasonable examiner would have considered EPA-1929 important in a patentability determination of the '740 application. This is particularly so in view of the ' 740's prosecution history.

Specifically, the language UC originally used in claims two and five undoubtedly would have warranted the broad reading UC advocates. Original claim two claimed

[a] DNA transfer vector comprising a deoxynucleotide sequence coding for human proinsulin.

UC Ex. 3 at A000036. Original claim five claimed

[a] DNA transfer vector comprising a deoxynucleotide sequence coding for human proinsulin comprising a plus strand having the sequence:

[selected from among all possible DNA sequences encoding human proinsulin].

*Id.* at A000037. Lilly expert Armitage testified that claims two and five initially were "essentially identical claims. . . ." Tr. at 1741. We agree with Armitage's conclusion.

Importantly, the proposed broad language of claim five was not narrowed until June of 1983, when the PTO examiner mandated such amendment before allowing issuance of the '740 patent. UC Ex. 3 at A000254. Up until that time, UC had been prosecuting its '740 patent application -- an application that necessarily encompassed claim six of EPA-1929 -- without citing EPA-1929 to the PTO examiner.

UC argues that its evidence of subjective good faith effectively overcomes Lilly's allegations of intent to mislead. Specifically, UC asserts, its provocation of an interference proceeding between the Itakura and Riggs disclosure and another of UC's patents being prosecuted during the relevant time period is evidence of UC's lack of intent to deceive. UC posits that because the same examiner was handling both the interference proceeding and the prosecution of the '740 patent, UC could not be intending to mislead the examiner. Moreover, UC contends that the dates on certain of the evidence Lilly offered at trial indicates that many of the documents on which Lilly relies for its inequitable conduct charge predate the prosecution of the '740 patent. UC opines that because the correspondence was transmitted before the prosecution of the '740, the matters contained therein could not be associated with the '740 patent.

UC's arguments countering intent to mislead are not sufficient to overcome EPA- 1929's high level of materiality and the evidence of record clearly illustrating that UC knew of that materiality.

Preliminarily, we note that UC's provocation of the interference proceeding played a role in the Court's earlier denial of summary judgment on the issue of inequitable conduct. However, trial presented the Court with an opportunity to hear all the evidence; to determine the issue of materiality; and to judge the credibility of the witnesses. With this background, we now find that UC's provocation of an interference proceeding involving the Itakura and Riggs disclosure does not have the significance UC urges. We are unconvinced that bringing that disclosure to the attention of the PTO examiner in the context of a *different* patent application somehow justifies UC's failure to bring the disclosure to the attention of the PTO examiner in the context of the '740 patent application. Certainly, one could readily draw the inference that UC representatives pitted the Itakura and Riggs reference against a different patent application in an attempt to divert the examiner's attention from the relationship between the '740 application and the Itakura and Riggs disclosure.

UC's second offering of evidence on the issue of subjective good faith fares no better. It is true, as UC recognizes, that some of the evidence Lilly offered on the issue of inequitable conduct predates the file date of the '740 patent application. Greenlee testified that he could not remember having received ***1258** any information from UC pertaining to the cloning of human proinsulin prior to July 18, 1979; some pieces of the correspondence Lilly offered into evidence are dated in June of 1979.

For purposes of this discussion, we assume that Greenlee's testimony is accurate and that his written request for, *inter alia*, a copy of EPA-1929 initially was not spurred by UC's ensuing application for the '740 patent. Nonetheless, we cannot overlook the fact that Greenlee received EPA-1929 in late June of 1979 -- less than one month before his acknowledged receipt of information related to the '740 patent application. Moreover, given the clarity of the language of EPA-1929's claim six -- in which the inventors claim human proinsulin -- it is inconceivable that Greenlee, or other UC representatives to whom a copy of EPA-1929 was forwarded, did not shortly thereafter connect this claim with the material ultimately submitted in the '740 patent application. More importantly, the fact remains that UC representatives repeatedly were advised of the significant link between EPA- 1929 and the '740 patent application after prosecution of the latter had begun. Consequently, we are not persuaded that UC sufficiently has proved subjective good faith in its effort to counter Lilly's clear and convincing evidence of intent to mislead. The Court finds that UC's inequitable conduct in the prosecution of the '740 patent renders that patent unenforceable.

IV. *Conclusion*

In sum, we find that Lilly infringes neither the '525 patent nor the ' 740 patent; that the '525 patent's claims to the mammalian and vertebrate genera and to the human species are invalid for lack of an enabling disclosure; that were we to accept UC's offered interpretation of the broad claims in the '740 patent (an interpretation we have rejected), those claims would be invalid as anticipated; that the '525 and '740 patents are unenforceable based on UC's inequitable conduct. Judgment will be entered this day in accordance herewith.

FN1 Dorland's Medical Dictionary (27th ed. 1988).

FN2 An enzyme called reverse transcriptase is used for this process.

FN3 For additional information concerning the science underlying recombinant DNA technology, see *In re O'Farrell,* 853 F.2d 894 [ 7 USPQ2d 1673 ] (Fed. Cir. 1988).

FN4 This test determines the (in)substantiality of the differences between the claimed and accused products or processes by examining if the accused product or process " 'performs substantially the same function in substantially the same way to obtain the same result.' "*Hilton Davis,* 62 F.3d at 1518 (quoting *Sanitary Refrigerator Co. v. Winters,* 280 U.S. 30, 41-42 [ 3 USPQ 40 ] (1929)).

FN5 According to the specification of the

'740 patent, a plasmid is an example of a transfer vector commonly used in bacterial genetics. A vector is "a DNA molecule which contains genetic information which insures its own replication when transferred to a host microorganism strain." UC Ex. 1 at col. 4, ln. 25.

FN6 Dr. Gilbert is a 1980 Nobel Laureate in chemistry and the author or co-author of some 123 articles on various phases of molecular biology.

FN7 Cloning is defined as "the formation of a clone." Dorland's Medical Dictionary at 346. (27th ed. 1988). DNA cloning is defined as "in genetics, the production of many identical copies of a specific DNA fragment."*Id.* at 346-47. Clone is defined as, *inter alia,* "a DNA population derived from a single hybrid DNA molecule (recombinant vector, *q. v.*) by replication in a eukaryotic or bacterial host cell."*Id.* at 346.

FN8 The ' in "5 ' " stands for prime, and the 5 ' region is the area upstream of (or preceding) the DNA coding for human proinsulin.

FN9 Research leading to the application for the '525 patent was conducted in the rat. At the time the application for the '525 patent was filed, human proinsulin cDNA had not been isolated and characterized.

FN10 We have combined consideration of claims five and six because claim six is dependent upon claim five. If claim five literally is not infringed, neither is dependent claim six.

FN11 At least during the relevant time period, an alternative method for producing the desired product was called direct expression. With direct expression, there was no fusion of a protective bacterial protein to the desired product. Hence, the desired product was expressed directly -- with no subsequent need for cleaving. *See* UC Ex. 1 at cols. 9-10 (explaining differences between two types of expression).

FN12 The examiner cited Ullrich *et al.*, Villa-Komaroff *et al.*, Cohen *et al.*, and Crea *et al.* as prior art that mandated rejection of claims one through eleven. The examiner's reference to Ullrich *et al.* included two articles: "Rat Insulin Genes: Construction of Plasmids Containing the Coding Sequences," 196 *Science* 1313-19 (June 17, 1977) (authors are Ullrich, Shine, Chirgwin, Pictet, Edmund Tischer, Rutter and Goodman), *see* UC Ex. 98; and "The Structure and Expression of the Insulin Gene," *Proceedings of the Symposium on Proinsulin, Insulin and C-Peptide, Tokushima* at 20-26 (July 1978), Lilly Ex. 3180. The Villa-Komaroff *et al.* article the examiner cited was: "A Bacterial Clone Synthesizing Proinsulin," 75 *Proceedings of the Nat'l Academy of Sciences* 3727-31 (Aug. 1978) (authors are Lydia Villa-Komaroff, Argiris Efstratiadis, Stephanie Broome, Peter Lomedico, Richard Tizard, Stephen Naber, William Chick and Walter Gilbert). *See* Lilly Ex. 3182.

In his reference to Crea *et al.*, the examiner was citing "Chemical Synthesis of Genes for Human Insulin," 75 *Proceedings of the Nat'l Academy of Sciences* 5765-69 (Dec. 1978) (authors are Roberto Crea, Adam Kraszewski, Tadaaki Hirose and Keiichi Itakura). *See* Lilly Ex. 3100. The examiner's Cohen *et al.*, reference was to United States Patent Number 4,237,224, entitled "Process for Producing Biologically Functional Molecular Chimeras." The patent's application was filed on January 4, 1979, and the patent issued on December 2, 1980. The inventors are Stanley Cohen and Herbert Boyer. *See* Lilly Ex. 2260.

FN13 These experts also testified that the

Crea *et al.*, article and Ullrich *et al.*, *Symposium* article describe the production of fusion protein DNA sequences. Tr. at 1619, 1628, 1799.

FN14 Claim six of EPA-1929 claims, *inter alia,* a plasmid comprising a fusion protein encoding human proinsulin, in which the bacterial portion of the fusion protein is homologous to the bacterial host into which the plasmid will be inserted and the human proinsulin portion is a polypeptide heterologous to the bacterial host. As a model, the EPA-1929 inventors used the heterologous polypeptide somatostatin, chemically synthesizing that gene. The inventors further state that their synthesizing techniques can be used to code for "virtually any known amino acid sequence." Lilly Ex. 3047 at 11. The authors of EPA-1929 specifically reference human proinsulin in the body of their publication and indisputably claim human proinsulin, as well as various other polypeptides, in claim six. Lilly Ex. 3047.

UC argues that EPA-1929 was less relevant prior art than other prior art it cited to the examiner. UC also contends that a portion of the amino acid sequence for human proinsulin was unknown prior to the application for the '740 patent. If this were so, EPA-1929's claim to human proinsulin would be invalid as nonenabling. We only need state at this point that we disagree with UC's position. These issues will be discussed, *infra,* in detail.

FN15 Some information pertaining to patent claim drafting is in order. There are three parts to a claim: the preamble, the transition and the body. The transition is the part with which we currently are concerned. Generally, there are three categories of transitions. *See* D. Chism, Patents, Section 8.06 [1] at 8-99. An open-ended transition is recognized by use of the term "comprising" or the phrase "which comprises."*Id.* at 8-100-8-101. A closed-ended transition employs either the phrase "consisting of" or the phrase "which consists of."*Id.* Finally, the intermediate transition, sometimes referred to as nearly closed-ended, is identified by either the phrase "consisting essentially of" or "which consists essentially of."*Id.* at 8-10-2. The intermediate transition excludes "additional, unspecified components that would affect the basic and novel characteristics of the product defined in the balance of the claim."*Id.*

We note that claim five of the '740 patent includes both the term "comprising" and the phrase "consisting essentially of." "Comprising," however, is used in claim five to qualify that which the transfer vector may contain, while the phrase "consisting essentially of" limits that which the DNA sequence coding for human proinsulin may contain. This case more narrowly focuses on the content of the DNA insert coding for human proinsulin. Hence, the more restrictive transition is applicable to the ensuing discussion.

FN16 Claims twenty-two and twenty-four claimed as follows:

--22. A fusion protein comprising the complete amino acid sequence of human proinsulin as its C-terminus sequence,

a portion of a prokaryotic protein as its N-terminus sequence, and

joining the C-terminus and N-terminus sequences, an intermediate segment at which the fusion protein can be cleaved enzymatically to release full- sequence proinsulin free of the N-terminus sequence.

--24. The protein of claim 22 wherein the intermediate segment is a polylysine segment, and the protein can be selectively cleaved by digestion with carboxypeptidase B or cathepsin B, to release full-sequence human proinsulin from the lysine residues and attached N-terminus sequence.--

Lilly Ex. 3030 at OFW 798-99. Claim twenty-three is not relevant to our discussion.

FN17 The '246 patent is entitled "Method for Microbial Polypeptide Expression," and its inventor is Arthur Riggs. The application for the ' 246 patent has an application date of November 8, 1977; the patent issued on December 28, 1982.

FN18 We discuss this issue in detail at pages 46 through 65.

FN19 Claims two, three, thirteen and fourteen of the '740 patent read:

2. A DNA transfer vector comprising an inserted cDNA consisting essentially of a deoxynucleotide sequence coding for human proinsulin, the plus strand of said cDNA having a defined 5 ' end, said 5 ' end being the first deoxynucleotide of the sequence coding for said proinsulin.

3. A microorganisms [sic] transformed by the transfer vector of claim 1 or 2. . . . 13. The DNA transfer vector of claim 5 wherein:

[DNA sequence encoding the natural sequence (cDNA) for human proinsulin].

14. The DNA transfer vector of claim 5 wherein the codon for amino acid position one is preceded by 5 '-ATG and

[DNA sequence encoding for a semisynthetic human proinsulin protein].

UC Ex. 1 at cols. 16-20.

FN20 Claim three is dependent on claim two, and claim thirteen describes a transfer vector containing the same sequence for human proinsulin as found in claim two. Thus, if claim two is not infringed under the doctrine of equivalents, neither is claim three nor claim thirteen.

FN21 The reason for this limitation is discussed in more detail in this Opinion in the preceding section regarding literal infringement and the following section concerning validity.

FN22 Lilly previously argued the inadequacy of UC's written description in a summary judgment motion. The Court denied that motion, reasoning that further development of the record should precede a determination of the issue.

FN23 These claims in the '525 patent read:

1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

2. A recombinant procaryotic microorganism modified to contain a nucleotide sequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin. . . . 4. A microorganism according to claim 2 wherein the vertebrate is a mammal. . . . 6. A plasmid according to claim 2 comprising a plasmid containing at least one genetic determinant of col E1.

7. A microorganism according to claim 2 comprising a strain of *Escherichia coli.*

FN24 Claims five of the '525 patent claims:

5. A microorganism according to claim 2 wherein the vertebrate is a human.

FN25 "Conception is the 'formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice.' "*Amgen,* 927 F.2d at 1206 (quoting *Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1376 [ 231 USPQ 81 ] (Fed. Cir. 1986), *cert. denied,* 480 U.S. 947 (1987)) (further citations omitted). "Conception requires both the idea of the invention's structure and possession of an operative method of making it."*Amgen,* 927 F.2d at 1206 (citation omitted).

FN26 A codon consists of three nucleotides. A nucleotide consists of a base chemical that is linked to a 5-carbon sugar that has a phosphate group attached. *See In re O'Farrell,* 853 F.2d at 896.

FN27 Ironically, the PTO examiner did not permit UC to claim the untailored cDNA For human proinsulin in UC's later prosecution of the '740 patent, even though UC scientists actually had isolated and characterized that structure prior to filing that patent application. The examiner's rejection was based in part on the Ullrich *et al. Science* article, which formed the basis for the '525 patent. Our present determination that UC had not described adequately human proinsulin cDNA in the '525 specification indicates that the human proinsulin cDNA in its untailored state likely would have been patentable to UC over the Ullrich *et al.,* reference. Even if UC had garnered the untailored cDNA sequence for human proinsulin in its prosecution of the '740 patent, however, the result in this Opinion nevertheless would remain unchanged because, as we stated *supra,* (1) Lilly does not use the cDNA sequence in its manufacture of human (pro) insulin; and (2) Lilly uses a fusion protein in its manufacture of human (pro) insulin rather than a sequence coding for direct expression.

FN28 This is not the first time that the issue of anticipation has been before this Court. Previously, Lilly moved for summary judgment of claims five and six of the '740 patent, arguing that the amino acid sequence for human proinsulin was within the common knowledge of technologists in the field before the date of the application for the '740 patent. Genuine issues of material fact dictated a denial of Lilly's motion.

FN29 As stipulated in 35 U.S.C. Section 102,

[a] person shall be entitled to a patent unless--

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, . . . .

FN30 EPA-1929 bears a publication date of May 16, 1979. The application for the '740 patent has a file date of September 12, 1979. Hence, EPA-1929 is prior art to the '740 patent.

FN31 The following exhibits, the dates of which predate the application for the '740 patent, included the amino acid sequence for human proinsulin: Lilly Ex. 3118 at 1384; Lilly Ex. 3124 at 326; Lilly Ex. 3130 at 127; and Lilly Ex. 3131 at 151.

FN32 According to Lilly, the C-peptide functions to bring the A-chain and the B-chain in close proximity so that they will interact to form correct disulfide bonds.

FN33 EPA-1929 actually was filed November 6, 1978.

FN34 The authors of the article are Philip

E. Oyer, Sooja Cho, James D. Peterson and Donald F. Steiner, of the University of Chicago, Department of Biochemistry.

FN35 The results of this experiment formed the basis for UC's '525 patent.

FN36 Gilbert is referring to the nucleotide sequence in the natural source, rather than the amino acid sequence for which the nucleotide sequence codes.

FN37 The greater the likelihood of such a change occurring, the lesser the likelihood that the amino acid sequence for human proinsulin was known at the time in question.

FN38 UC's expert Richards testified that a mutation has been reported in the literature. That mutation was a single point mutation in one of the arginines in the dog. We note, however, that this single point mutation, which did not change the amino acid for which the codon codes, is the only species of mammal in which there has been any mutation spanning the 80 million years of mammalian history. Tr. at 2035-36.

FN39 The amino acid sequence of human proinsulin reported in the Oyer *et al.* article was based on a combination of direct and indirect evidence. The C-peptide was determined via direct evidence from Edman degradation analysis. The dibasic residues, located at the ends of the C-peptide, were determined via indirect evidence. This indirect evidence included (l) compositional studies of intact human proinsulin establishing that these residues consisted of three arginine amino acids and one lysine amino acid, and (2) the sequencing evidence from other mammalian species, in conjunction with knowledge of the high conservation of the dibasic residues among mammalian species.

FN40 This paper is entitled "Rat Insulin Genes: Construction of Plasmids Containing the Coding Sequences" and, as we stated earlier in this Opinion, provides the basic disclosure found in the '525 patent

FN41 It appears that some scientists included the dibasic residues with the C-peptide, while others considered the dibasic residues as separate from the C-peptide. The text of the '740 patent illustrates that the UC scientists included the dibasic residues within the C-peptide.

FN42 Ziemer had become Ziemer Hartig by the time her deposition in this action was taken.

FN43 Significantly, as we earlier stated, Rutter and the other named inventors on the '740 patent included in their description of the C- peptide amino acids 31-65. This description includes the dibasic amino acid residues at each end of the C-peptide.

FN44 These regulations, however, did not pacify everyone. Public debate in Cambridge, Massachusetts about the safety of recombinant DNA research led to a determination that such research was banned from "the City of Cambridge until the citizens of Cambridge and the city council had convinced themselves that it was safe for the research to continue." Tr. at 1299. A citizens committee was appointed to investigate the matter and, in early 1977, the ban was lifted. Tr. at 1299-1300.

FN45 Rutter and Goodman were co-principal investigators for the research in issue in the instant case. Lilly. Ex. 3420 at HG 002873. Rutter was then chairman of the Department of Biochemistry and Biophysics at the University of California.

Tr. at 106; Lilly Ex. 3554A at 200. Goodman was then a professor in the Department of Biochemistry at the University. Tr. at 1106. During some of the time in which the subject research was being conducted, Goodman was out of the country on sabbatical leave. His absence, however, is not relevant to this discussion.

FN46 An institutional biohazard committee was established in each institution that received NIH funding. According to the guidelines, such a committee was responsible for, *inter alia*, certifying, and recertifying annually, to NIH that the facilities, procedures, practices, training, and expertise of involved personnel had been reviewed and approved. Lilly Ex. 3547 at HG2 580781.

FN47 Hearings before a subcommittee of the United States Senate were held in November of 1977 to examine the potential need for federal regulation governing all recombinant DNA research, including research not funded by the NIH. Lilly Ex. 3554A. At the hearings, Rutter testified about the pBR322 incident. *Id.* at 200-24. Rutter told the subcommittee, *inter alia*, that the application for the '525 patent was not based on PBR322 research, *id.* at 217-18, and that there were no commercial interests motivating UC to use the uncertified plasmid. *Id.* at 219.

FN48 The record suggests that Goodman actually became aware of the uncertified status of pBR322 on March 1, 1977. Lilly Ex. 3400 at WR 10052. Reportedly, on March 4, 1977, Goodman informed Rutter of the matter. *Id.*

FN49 The way in which ORDA became aware of the pBR322 incident is discussed *infra* at 73-74.

FN50 In identical letters Rutter and Goodman exchanged with each other in March of 1977, discussed *infra*, they state that on March 5, 1977, Ullrich destroyed the "plasmid containing cells and kept only the purified DNA from the clones. . . ." Lilly Ex. 3361 at HG 000691; Lilly Ex. 3363 at WR 10720.

FN51 Gilbert also relied on Goodman's notes of a March 14, 1977, meeting with Lilly. Tr. at 1315-16; Lilly Ex. 3349. At this meeting, Goodman had drawn on the board a plasmid labeled in the same fashion as one in Goodman's insulin experiment folder. Lilly Ex. 3349 at HG 001462. In the experiment folder, the drawing appears under the title, "clone 1-13." Lilly Ex. 3354 at HG 002081. The Goodman- Lilly meeting was on March 14, 1977. Hence, Gilbert concluded that the sequence listed in Goodman's insulin experiment had to exist before that date. Because Rutter testified that UC experiments with plasmid pCR1 were ineffective, tr. at 137, and because pMB9 was not even certified for use until April 18, 1977, the sequence described in Goodman's insulin experiment folder, and later drawn on the board at the Lilly meeting, had to be a pBR322 sequence. Tr. at 1328.

FN52 At trial, Lilly introduced certain drafts of research manuscripts found in UC's files. Lilly contends that although these manuscripts purport to arise from research conducted with certified plasmids, yet the data contained therein illustrate that the manuscripts actually were based on work done with the uncertified vector pBR322.

We agree with Lilly that the record illustrates that the data contained in these manuscripts originated in pBR322 research work. However, we already have found that the research work reported in the *Science* article and, ultimately, in the '525 patent, is based, at least in part, on work done in the uncertified plasmid. Thus, while the common

threads in these manuscripts (e.g., identical sequencing errors, identical typographical errors) strengthen Lilly's argument that the manuscripts all rely upon pBR322 research work, a detailed explanation of those documents and their corresponding features is unnecessary for purposes of this decision.

FN53 Genentech, a corporation located in California, is involved in other of the six cases consolidated in this Court for pretrial proceedings by the Judicial Panel on Multidistrict Litigation. *See, supra* at 1-2.

FN54 At trial, Goodman verified that the notes were in his handwriting. Tr. at 1219.

FN55 Evidence of record convinces us that Goodman was referring to pBR322 when he named the "Boyer plasmid." Ullrich testified that scientists in Herb Boyer's laboratory developed pBR322. Tr. at 797-98. Moreover, other testimony reveals that the only plasmid with which UC researchers had achieved success by March of 1977 was the uncertified pBR322. Specifically, Rutter averred that UC was unsuccessful in its attempts to clone in plasmid pCR1. Tr. at 137. Furthermore, Rutter stated that UC researchers did not begin using vector pMB9 until after it was approved by the NIH. Tr. at 136. That approval was not received until April of 1977. Consequently, Goodman's mid-March 1977 reference to "Boyer plasmid" must mean pBR322.

FN56 It also is interesting to note that by agreement with UC the inventors are entitled to 50 percent of the net profits derived from any royalties or fees received from patent rights.

FN57 Lilly contends that UC's inequitable conduct in procurement of the '525 patent should render the '740 patent unenforceable as well. However, we believe UC acted inequitably in the prosecution of the '740 patent itself, as discussed *infra*. Therefore, we need not consider whether UC's conduct associated with the '525 patent should hinder its ability to enforce another patent in suit.

FN58 Lilly brought this issue before the Court previously in its third motion for summary judgment. In an Entry deciding that motion, we concluded that summary resolution of Lilly's allegations of inequitable conduct in the context of the '740 patent prosecution would be improper.

FN59 The original United States application included techniques for chemically synthesizing DNA and a specific claim to DNA constructions containing a gene for human proinsulin. The November 1979 embellishment added to the patent application examples describing the separate A- and B- chain insulin work.

FN60 This evaluation is entitled "Evaluation of the United States Patent Position of the University of California With Respect to DNA Recombinant Technology."

FN61 Greenlee was an attorney with the law firm Irons and Sears when he first began patent work for the University of California. Tr. at 909. He continued that work at Keil & Witherspoon. *Id.*

FN62 Greenlee testified that during the time he was responsible for the University's United States prosecution work, he corresponded with UC'S then patent administrator Roger Ditzel (now deceased), and with the inventors of the patents. Tr. at 1024.

S.D.Ind.

39 U.S.P.Q.2d 1225
1995 WL 735547 (S.D.Ind.)
**(Cite as: 39 U.S.P.Q.2d 1225)**

39 U.S.P.Q.2d 1225

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65 U.S.P.Q.2D 1385
314 F.3d 1313
**(Cite as: 65 U.S.P.Q.2d 1385)**



**H**

Amgen Inc.
v.
Hoechst Marion Roussel Inc.

U.S. Court of Appeals Federal Circuit

Nos. 01-1191, -1218

Decided January 6, 2003

United States Patents Quarterly Headnotes

**PATENTS**

**[1] Patent construction -- Claims -- Broad or narrow (§ 125.1303)**

Claims directed to production of recombinant erythropoietin are not limited to use of exogenous DNA, even though specification states that invention is "uniquely characterized" by host cells' expression of "exogenous DNA sequences," and examiner stated that application "teaches and enables only cells that have been transformed with exogenous DNA," since none of asserted claims contain express limitation to either "exogenous DNA" or "endogenous DNA," since doctrine of claim differentiation precludes narrow construction of asserted claims, and since examiner's comment was made in context of rejection based on failure to teach high EPO production required by claims, not failure to teach transformation with exogenous EPO.

**[2] Patent construction -- Claims -- Broad or narrow (§ 125.1303)**

**Patent construction -- Claims -- Defining terms (§ 125.1305)**

Terms "non-naturally occurring," "vertebrate cells," and "mammalian cells," as used in claims directed to production of recombinant erythropoietin, are properly construed to include human cells, since there is heavy presumption that claim term carries its ordinary and customary meaning, and prosecution history may not be used to infer intentional narrowing of claim absent clear disavowal of claim coverage, and since specification can be fairly read to disclose use of human DNA in human host cells in culture.

**[3] Patent c nstruction -- Claims -- Broad or narrow (§ 125.1303)**

**Patent construction -- Claims -- Process (§ 125.1309)**

Asserted claims directed to production of recombinant erythropoietin are properly construed as "pure" product claims directed to structural entity that is not defined or limited by how it is made, since prosecution history contains strong evidence that both patentee and examiner viewed issued claims as lacking process component, and since "source" limitations in claims merely exclude human EPO from specific sources, without restricting claimed EPO to that produced from any particular source or by any particular method.

**[4] Patentability/Validity -- Specification -- Written description (§ 115.1103)**

Asserted claims directed to production of recombinant erythropoietin are not invalid for failing to describe use of exogenous human EPO DNA in human cells, since, for claim drawn to composition rather than process, written description requirement does not demand that specification describe technological developments in manner in which claimed composition is made that may arise after application is filed.

**[5] Patentability/Validity -- Specification -- Written description (§ 115.1103)**

Asserted claims directed to production of recombinant erythropoietin are not invalid for failing to sufficiently describe all vertebrate and mammalian cells as engineered in claimed invention, even though precise definitions of DNA sequences are not disclosed, since terms "vertebrate" and "mammalian" are used to identify types of cells that can be employed to produce human recombinant EPO, not undescribed, previously unknown DNA sequences, and since terms therefore readily convey distinguishing information concerning their identity, such that one of ordinary skill in art could visualize or recognize identity of members of genus.

**[6] Patentability/Validity -- Specification -- Written description (§ 115.1103)**

Claims directed to production of recombinant erythropoietin are not rendered invalid by alleged failure to disclose use of endogenous EPO DNA to make claimed compounds, since endogenous activation is merely different method of making claimed composition, and since patentee need only describe invention as claimed, and need not describe unclaimed method of making claimed

product; although patentee stated during prosecution that its invention is "uniquely characterized" by exogenous expression of DNA, such statements do not clearly indicate that exogenous expression is only possible mode of invention, or that other methods were outside stated purpose of invention.

**[7] Patentability/Validity -- Specification -- Enablement (§ 115.1105)**

Claims of patents directed to production of recombinant erythropoietin are not rendered invalid for lack of enablement by failure of specifications to describe production of EPO using human cells or endogenous human EPO DNA, since method is immaterial to claims at issue, and enablement inquiry therefore does not require specification to describe technological developments concerning method of making composition that arose after patent application was filed, and since rule that specification need teach only one mode of making and using claimed composition renders failure to disclose later-developed endogenous activation technology legally irrelevant.

**[8] Patentability/Validity -- Specification -- Claim adequacy (§ 115.1109)**

Claims for recombinant erythropoietin product that require product to have "glycosylation which differs from that of human urinary erythropoietin" are invalid for indefiniteness, since glycosylation of uEPO must be known with certainty before it can be determined whether claimed glycoprotein has glycosylation different from that of uEPO, but specification does not direct those of ordinary skill in art to standard by which appropriate comparison can be made, and since this ambiguity in claim scope is central to definiteness requirement of 35 U.S.C. § 112.

**[9] Infringement -- Literal infringement (§ 120.05)**

**Infringement -- Defenses -- Prosecution history estoppel (§ 120.1105)**

Claims for recombinant erythropoietin product, in which EPO glycoprotein "comprises the mature erythropoietin amino acid sequence" shown in figure depicting 166 amino acids, is not literally infringed by accused EPO product in which glycoprotein contains only 165 amino acids, even though research conducted after patent was drafted demonstrated that full sequence for mature EPO is actually 165 amino acids, since specification states that figure in question serves to identify primary structural conformation of mature human EPO "as including 166 specified amino acid residues," and since this statement, and use of term "comprising" in claims, means that claimed glycoprotein must have, at minimum, all 166 amino acid sequences shown in figure; finding that claims are infringed under doctrine of equivalents must be vacated, since "mature amino acid sequence" limitation was added to overcome rejection for "same invention" type double patenting, and since narrowing amendment made to satisfy any requirement of Patent Act may give rise to prosecution history estoppel.

**[10] Infringement -- Construction of claims (§ 120.03)**

**Patent construction -- Claims -- Process (§ 125.1309)**

Summary judgment that claims directed to process for producing glycosylated erythropoietin are not infringed by accused process must be vacated, since federal district court compared accused process by reference to examples, rather than claimed process, and in doing so failed to abide by cardinal principle that accused process must be compared to claims, rather than to preferred or commercial embodiment.

**[11] Infringement -- Construction of claims (§ 120.03)**

**Patent construction -- Claims -- Broad or narrow (§ 125.1303)**

Claimed pharmaceutical composition containing erythropoietin, in which EPO is "purified from mammalian cells grown in culture," does not require that EPO product be recovered directly from cell, rather than from cell culture medium, since undisputed preferred embodiment of invention contemplates purification of EPO from culture medium, and this preferred embodiment cannot be read out of claims.

**[12] Infringement -- Doctrine of equivalents -- Reverse equivalents (§ 120.0703)**

Accused product infringes claims directed to vertebrate cells grown in culture and capable of producing erythropoietin, even though it is undisputed that method by which defendants control DNA transcription in accused cells is not identical to transcription method used in claimed cells, since claim limitation to "control[ling] transcription of DNA encoding human erythropoietin" is nevertheless met literally by accused cells, in which cytomegalovirus performs function of initiating and regulating process of transcription.

**[13] Patentability/Validity -- Anticipation -- Prior art (§ 115.0703)**

**Patentability/Validity -- Obvi usness -- Relevant**

**prior art -- Particular inventions (§ 115.0903.03)**
**Patent construction -- Claims -- Defining terms (§ 125.1305)**
Federal district court's finding that study is not prior art to claims directed to production of recombinant erythropoietin, based on court's conclusion that study failed and thus did not show claimed "therapeutically effective" use of EPO, must be vacated, since, if term encompasses patient responses described in specification, then study may constitute invalidating prior art even if it did not achieve intended result, and since term "therapeutically effective" was not considered during Markman hearing, and district court should have opportunity to construe term in first instance.
**[14] Patentability/Validity -- Anticipation -- Prior art (§ 115.0703)**
**Patentability/Validity -- Specification -- Enablement (§ 115.1105)**

**JUDICIAL PRACTICE AND PROCEDURE**
**Procedure -- Burden of proof (§ 410.35)**
Infringement defendant is entitled to have federal district court presume enablement of claimed and unclaimed subject matter in prior art patent that defendant asserts as invalidating prior art, and court therefore cannot ignore asserted patent, in evaluating defense of invalidity for anticipation, simply because defendant has not proven it enabled; thus, burden rests on patentee to prove nonenablement of prior patent, not on defendant to prove enablement, but if patentee presents evidence of nonenablement that district court finds persuasive, then presumption has been overcome, and court must exclude that reference from anticipation inquiry.

**PATENTS**
**[15] Patentability/Validity -- Specification -- Enablement (§ 115.1105)**
**Patentability/Validity -- Obviousness -- Relevant prior art -- In general (§ 115.0903.01)**
Prior patent need not be enabled to qualify as prior art under 35 U.S.C. § 103; therefore, federal district court cannot disregard asserted prior patent, in evaluating defense of invalidity for obviousness, on ground that patent is not enabled.

**PATENTS**
**Particular patents -- Chemical -- Erythropoietin**
5,547,933, Lin, production of erythropoietin, judgment of noninfringement as to claims 1, 2, and 9 vacated; judgment of invalidity affirmed; judgment that claims are not unenforceable, affirmed.
5,618,698, Lin, production of erythropoietin, judgment of noninfringement as to claims 4-9 vacated; judgment that claims are not unenforceable, affirmed.
5,621,080, Lin, production of erythropoietin, judgment that claims 2-4 are infringed under doctrine of equivalents vacated; judgment that claims are not invalid, vacated; judgment that claims are not unenforceable, affirmed.
5,756,349, Lin, production of erythropoietin, judgment of infringement as to claims 1, 3, 4, and 6 affirmed; judgment of noninfringement as to claim 7 vacated; judgment that claims are not invalid, vacated; judgment that claims are not unenforceable, affirmed.
5,955,422, Lin, production of erythropoietin, judgment of infringement as to claim 1 ***1388** affirmed; judgment that claims are not invalid, vacated; judgment that claims are not unenforceable, affirmed.

Appeal from the U.S. District Court for the District of Massachusetts, Young, C.J.; 57 USPQ2d 1449.

Action by Amgen Inc. against Hoechst Marion Roussel Inc., n/k/a Aventis Pharmaceuticals Inc., and Transkaryotic Therapies Inc. for patent infringement, and for declaratory judgment that defendants will infringe plaintiff's patents in future. Following Markman hearing and bench trial, district court construed claims at issue, held some claims of five patents in suit to be not invalid and infringed, and found others to be invalid and/or not infringed. Parties cross- appealed. Affirmed in part, vacated in part, and remanded; Clevenger, J., dissenting in part in separate opinion.

Lloyd R. Day Jr., David M. Madrid, Robert M. Galvin, Terry L. Tang, Paul S. Grewal, Richard C. Lin, Jonathan Loeb, Jackie N. Nakamura, and Matthew E. Hocker, of Day Casebeer Madrid & Batchelder, Cupertino, Calif.; Edward M. O'Toole, of Howrey Simon Arnold & White, Chicago, Ill.;

Stuart L. Watt, Wendy A. Whiteford, Steven M. Odre, Monique L. Cordray, and Robert R. Cook, of Amgen Inc., Thousand Oaks, Calif.; D. Dennis Allegretti and Richard M. Wong, of Duane, Morris & Heckscher, Boston, Mass., for plaintiff-cross appellant.

Hebert F. Schwartz, Kenneth B. Herman, James F. Haley Jr., Denise L. Loring, Douglas J. Gilbert, Frances M. Lynch, Gerald J. Flattmann Jr., and Robert B. Wilson, of Fish & Neave, New York, N.Y.; Robert S. Frank Jr. and Eric J. Marandett, of Choate, Hall & Stewart, Boston; Michael J. Astrue and Mary S. Consalvi, of Transkaryotic Therapies Inc., Cambridge, Mass., for defendants- appellants.

Before Michel, Clevenger, and Schall, circuit judges.

Michel, J.

Plaintiff-Cross Appellant Amgen Inc. ("Amgen") is the owner of numerous patents directed to the production of erythropoietin ("EPO"), a naturally occurring hormone that controls the formation of red blood cells in bone marrow. Amgen markets and sells EPOGEN®, a highly successful commercial embodiment of the patented erythropoietin. Seeking to impede defendants-appellants Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc. (collectively "TKT") from commercializing a competitive EPO product, Amgen filed a declaratory judgment action in the United States District Court for the District of Massachusetts in April 1997, alleging that TKT's Investigational New Drug Application ("INDA") infringed United States Patent Nos. 5,547,933 ("the '933 patent"); 5,618,698 ("the '698 patent"); and 5,621,080 ("the '080 patent"). The complaint was amended in October 1999 to include United States Patent Nos. 5,756,349 ("the '349 patent") and 5,955,422 ("the '422 patent"), which issued after suit was filed.

After a three-day *Markman* hearing, the case was tried to the court for 23 days over the course of four months. In January 2001, the district court issued an exhaustive 244-page opinion in which it: (i) construed the disputed claims; (ii) held each of the patents enforceable; (iii) held the '080, '349 (product claims), and '422 patents valid and infringed; (iv) held the '698 patent not infringed; and (v) held the '933 patent not infringed or, in the alternative, invalid for failure to satisfy 35 U.S.C. § 112. *Amgen, Inc. v. Hoescht Marion Roussel, Inc.*, 126 F.Supp.2d 69, 57 USPQ2d 1449 (D. Mass. 2001). On appeal, TKT urges reversal on the grounds that the patents in suit are all unenforceable, that the district court's claim construction was erroneous, and alternatively, if that claim construction was correct, that the court's validity determinations were erroneous. Amgen asserts, in its cross appeal, that the district court committed error: (i) by comparing the accused process to the examples in the specification rather than the limitations of the method claims of the '349 and '698 patents; and (ii) by holding the '933 patent invalid for failure to comply with § 112. We heard oral argument on May 7, 2002.

We commend the district court for its thorough, careful, and precise work on what is indubitably a legally difficult and technologically complex case. There is no doubt that the court marshaled tremendous time and resources in its effort to reach correct results. Nevertheless, because we must conclude that the court committed certain errors of law in certain of its validity and infringement determinations, ***1389** we cannot affirm the judgment in its entirety.

We affirm *in toto* the district court's claim construction. We also affirm: (i) its determination that none of the patents in suit is unenforceable for inequitable conduct; (ii) its contingent determination that the '933 patent is invalid under § 112 ¶ 1; (iii) its grant of summary judgment of infringement of '422 patent claim 1; (iv) its determination that the '080, '933, '349, and '698 patents are not anticipated by the Sugimoto reference; and (v) its determination that '349 patent claims 1, 3-4, and 6 are infringed. Because the district court misapplied the law, however, we vacate: (i) its determination that the '933 patent is not infringed; (ii) its determination that the '080 patent is infringed under the doctrine of equivalents; (iii) its determination that the '080, '349, and '422 patents are not invalid; and (iv) its determination that the asserted method claims of the '698 patent and '349 patent claim 7 are not infringed.

65 U.S.P.Q.2D 1385
314 F.3d 1313
**(Cite as: 65 U.S.P.Q.2d 1385)**



Accordingly, we remand for the district court to reconsider: (i) whether the '080, '349, and '422 patents are obvious in light of the Sugimoto prior art or anticipated or obvious in light of the Goldwasser prior art; (ii) whether the '422 patent is anticipated by Sugimoto reference (and whether Amgen can prove its nonenablement); (iii) whether the asserted claims of the '698 patent and '349 patent claim 7 are infringed by the accused method; and (iii) whether the '080 patent is infringed under the doctrine of equivalents. In sum, as further explained in detail below, we affirm in part, vacate in part, and remand for further proceedings consistent herewith.

## BACKGROUND

As the district court set out in painstaking detail the basics of the underlying technology, we will provide only a brief summary here. The reader's familiarity with the fundamentals of molecular biology, genetics, and recombinant DNA technology necessary to this appeal is presumed. [FN1]

EPO is a naturally occurring protein that initiates and controls erythropoiesis, the production of red blood cells in bone marrow. Red blood cells are critical because they contain hemoglobin, a protein responsible for transporting oxygen from the lungs to peripheral tissues. Because EPO is produced in the kidney, patients with chronic kidney (renal) failure lack normal levels of EPO and, as a result, have a sub-optimal number of red blood cells -- a condition called anemia. The therapeutic goal for treating anemic patients is to increase the "hematocrit level," which represents the ratio of red blood cells to total blood volume, to normal or near-normal levels. This is accomplished through the introduction of additional EPO into the patient's system.

The implementation of this seemingly simple solution, introduction of exogenous EPO, proved to be difficult. Because human EPO is produced in very small amounts (even from the healthy human kidney), it is difficult to obtain by conventional methods. Early attempts to recover EPO from plasma or from human urine ("urinary EPO". or "uEPO") were unsuccessful because such recovery employed techniques that were complicated, yet still resulted in a low-yield, high-impurity, or unstable EPO end product. '933 patent, col. 6, line 60 -- col. 7, line 42. Similar attempts using antibody techniques failed because of difficulty in providing for the large-scale isolation of quantities of EPO from mammalian sources sufficient for further analysis, clinical testing, or therapeutic use. *Id.*, col. 9, lines 2-8. The first successful method of production of a therapeutically effective amount of erythropoietin used recombinant EPO ("rEPO") techniques; Amgen is recognized as the pioneer. *See, e.g., Molecular Biology and Biotechnology* at 108.

Amgen scientist Dr. Fu-Kuen Lin is the named inventor on all five patents in suit. Instead of attempting to purify EPO from natural sources, Lin isolated and characterized monkey and human EPO genes, then used conventional recombinant DNA technology to produce large amounts of rEPO. '933 patent, col. 13, lines 50-53. Lin was able to determine the entire DNA sequence of human EPO and from that, its predicted amino acid sequence. *Id.*, Fig. 6; col. 10, lines 65 -- col. 11, line 2. Using the isolated human EPO gene, Lin described several methods for producing therapeutically ***1390** effective amounts of human EPO using an expression vector. [FN2] *Id.*, col. 21, line 42 -- col. 25, line 27.

EPOGEN ®, the commercial embodiment of Amgen's patented EPO product, is produced by the method disclosed in patent specification Example 10. That example describes the production of human EPO through transfection (introduction) of exogenous DNA into host Chinese hamster ovary ("CHO") cells. The CHO host cell, using its own transcription machinery, then expresses human rEPO in abundance, which then accumulates in the host cell cytoplasm or in the culture media. *Id.*, col. 37, lines 43-49. The rEPO so recovered has the same or similar amino acid sequences and biological properties as naturally occurring human EPO, but differs in its "glycosylation," *i.e.*, in the patterns of branched carbohydrate chains that attach to the protein. '933 patent, col. 10, lines 34-41.

The patents in suit, which all claim priority to a December 1983 application long since abandoned, are continuations of a common ancestor -- United States Patent No. 4,703,008 -- which was at issue in this court's landmark decision in *Amgen Inc. v.*

*Chugai Pharm. Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991). [FN3] The '933 patent issued on August 20, 1996, containing 14 claims drawn primarily to a non-naturally occurring EPO product with certain characteristics. At issue in this lawsuit are claims 1, 2, and 9 (with the disputed claim terms here and below underscored):

1. A *non-naturally occurring erythropoietin glycoprotein* product having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having *glycosylation which differs from that of human urinary erythropoietin.*

2. The *non-naturally occurring EPO glycoprotein* product according to claim 1 wherein said product has a higher molecular weight than *human urinary EPO* as measured by SDS-PAGE.

9. A pharmaceutical composition comprising an effective amount of a glycoprotein product effective for erythropoietin therapy according to claim 1, 2, 3, 4, 5, or 6 and a pharmaceutically acceptable diluent, adjuvant or carrier.

The '698 patent issued on April 8, 1997, containing nine claims drawn to a process for producing a glycosylated erythropoietin polypeptide. At issue are claims 4-9:

4. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps:

a) growing, under suitable nutrient conditions, *vertebrate cells* comprising promoter DNA, other than human erythropoietin promoter DNA, *operatively linked to DNA* encoding *the mature erythropoietin amino acid sequence of FIG. 6*; and

b) isolating said glycosylated erythropoietin polypeptide expressed by said cells

5. The process of claim 4 wherein said promoter DNA is viral promoter DNA.

6. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:

a) growing, under suitable nutrient conditions, *vertebrate cells* comprising amplified *DNA encoding the mature erythropoietin amino acid sequence of FIG. 6*; and

b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.

7. The process of claim 6 wherein *said vertebrate cells* further comprise amplified marker gene DNA.

8. The process of claim 7 wherein said amplified marker gene DNA is Dihydrofolate reductase (DHFR) gene DNA.

***1391** 9. The process according to claims 2, 4 and 6 wherein said cells are *mammalian cells*.

The '080 patent, which issued with seven claims on April 15, 1997, claims both an isolated erythropoietin glycoprotein and a method for therapeutically administering a pharmaceutical composition thereof. Only product claims 2-4 are at issue:

2. An isolated erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises *the mature erythropoietin amino acid sequence of FIG. 6* and is not isolated from human urine.

3. A *non-naturally occurring erythropoietin glycoprotein* having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises *the mature erythropoietin amino acid sequence of FIG. 6.*

4. A pharmaceutical composition comprising a therapeutically effective amount of an erythropoietin glycoprotein product according to claim 1, 2, or 3.

The '349 patent, which issued on May 26, 1998, contains one method claim and six product claims that are drawn generally to types of vertebrate cells grown in culture. At issue are claims 1, 3-4, and 6-7:

1. *Vertebrate cells* which can be propagated in vitro and which are capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100 U of erythropoietin per 10 6cells in 48 hours as determined by radioimmunoassay, said cells comprising *non-human DNA sequences that control transcription of DNA encoding human erythropoietin.*

3. *Vertebrate cells* according to claim 1 capable of producing in excess of 1000 U erythropoietin per 106cells in 48 hours.

4. *Vertebrate cells* which can be propagated in vitro which comprise *transcription control DNA sequences*, other than human erythropoietin transcription control sequences, for production of human erythropoietin, and which upon growth in culture are capable of producing in the medium of their growth in excess of 100 U of erythropoietin per 10 6 cells in 48 hours as determined by radioimmunoassay

6. *Vertebrate cells* according to claim 4 capable of producing in excess of 1000 U erythropoietin per 106cells in 48 hours.

7. A process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, *vertebrate cells* according to claim 1, 2, 3, 4, 5, or 6.

Last, the '422 patent, containing two claims directed to therapeutically effective pharmaceutical compositions of EPO, was granted on September 21, 1999. Only claim 1 is in dispute:

1. A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is *purified from mammalian cells grown in culture.*

The district court conducted the *Markman* hearing in late March and early April 2000 in advance of Amgen's motion for summary judgment of infringement. The court entertained oral argument, aided by demonstrative exhibits, but heard no witness testimony and received no evidence. *Amgen* , 126 F.Supp.2d at 81, 57 USPQ2d at 1455. At the close of the hearing, the court announced its claim constructions from the bench; these oral rulings were included and expounded upon in the written opinion ruling on the merits following trial. *Id.* at 84- 94, 57 USPQ2d at 1457-64.

Immediately following the *Markman* hearing, the court turned to Amgen's pending motion for summary judgment of infringement of '422 patent claim 1 and '349 patent claims 1, 3-4, and 6. As to the '422 patent, the district court found: (1) that it was uncontradicted that the accused product, HMR4396, was a pharmaceutical composition; (2) that it necessarily contained a therapeutically effective amount of human erythropoietin (otherwise, the filing of an INDA would be pointless); and (3) that the record evidence demonstrated that HMR4396 contained a pharmaceutically acceptable diluent, adjuvant, or carrier as claimed in claim 1. *Id.* at 94-95, 57 USPQ2d at 1455-56. The sole remaining question was whether the accused erythropoietin product had been "purified from mammalian cells grown in culture." The court found, in light of its claim construction that the term "mammalian" ***1392** comprises human cells, that the last limitation had been met. *Id.* at 95-96, 57 USPQ2d at 1466. The court therefore granted summary judgment of infringement of '422 patent claim 1.

Trial commenced on May 15, 2000. When Amgen rested at the close of its infringement case, the court granted TKT's motions for judgment of non-infringement of the '698 patent and literal non-infringement of the '080 patent. *Id.* at 99-104, 57 USPQ2d at 1469-73. At the close of TKT's rebuttal case, the court granted Amgen's motion for judgment of validity, finding that TKT had not carried its burden of clearly and convincingly proving anticipation or obviousness. *Id.* at 104-17, 57 USPQ2d at 1473-82. The remaining issues were taken under advisement. The court's opinion issued on January 19, 2001, and these timely cross-appeals followed. Vested with jurisdiction under 28 U.S.C. § 1295(a)(1), we address below the myriad issues before us.

## DISCUSSION

### I

The rules are by now well known. Because claim language defines claim scope, the first step in an infringement analysis is to construe the claims, *i.e.*, to determine the scope and meaning of that which is allegedly infringed. *Markman v. Westview Instr., Inc.*, 52 F.3d 967, 976, 34 USPQ2d 1321, 1326 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370, 38 USPQ2d 1461 (1996). To properly construe the claims, a court must examine the claims, the rest of the specification, and, if in evidence, the prosecution history. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582, 39 USPQ2d 1573, 1576-77 (Fed. Cir. 1996). Thereafter, the properly construed claims are compared to the accused product or process to determine whether each of the claim limitations is met, either literally or equivalently. *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1365, 62 USPQ2d 1658, 1662 (Fed. Cir. 2002).

There are two general areas of dispute TKT raises regarding the district court's claim construction. First, TKT urges that the court erred by failing to limit the asserted claims to exogenous DNA, despite the fact that none of the claims in suit contain an "exogenous DNA" limitation. Second, TKT asserts that the court erred by refusing to limit the terms "vertebrate," "mammalian," and "non-naturally occurring" -- each of which appear in varying degrees within the asserted claims -- such that they exclude host human cells which, of course, are used by the accused infringers. We consider the trial court's claim construction -- a matter of law -- afresh on appellate review. *See Cybor Corp. v. FAS Tech., Inc.*, 138 F.3d 1448, 1455, 46 USPQ2d 1169, 1173 (Fed. Cir. 1998) ( *en banc*).

A

We turn first to address a threshold definitional dispute that carries with it important consequences for the infringement issues decided by the district court and facing us on appeal, to wit, what is the distinction between exogenous, as opposed to endogenous, DNA in recombinant DNA parlance? According to TKT, it practices an innovative process using homologous recombination: it takes the ordinarily unexpressed endogenous (or "native") EPO gene in human cells and transfects "a viral promoter and certain other DNA" that does not encode EPO. That "other" DNA is inserted into the chromosome at a pre- determined, targeted location upstream from the endogenous EPO gene to produce what TKT has termed "Gene-Activated EPO," or "GA-EPO." TKT contrasts this method with that of Amgen, which TKT asserts undeniably uses exogenous DNA.

None of the asserted claims contain either an "exogenous DNA" or "endogenous DNA" limitation. [FN4] Based upon representations allegedly made by Amgen during the prosecution of the patents in suit, however, TKT argues that many of the claims the district court construed should have been defined narrowly to include only exogenous DNA. The district court rejected this argument, as do we.

"It is the claims that measure the invention." *SRI Int'l v. Matsushita Elec. Corp.*, 775 F.2d 1107, 1121, 227 USPQ 577, 585 (Fed. Cir. 1985) ( *en banc*). Because the claims are best understood in light of the specification of which they are a part, however, courts must ***1393** take extreme care when ascertaining the proper scope of the claims, lest they simultaneously import into the claims limitations that were unintended by the patentee. *See, e.g., Hoganas AB v. Dresser Indus., Inc.*, 9 F.3d 948, 950, 28 USPQ2d 1936, 1938 (Fed. Cir. 1993) ("It is improper for a court to add extraneous limitations to a claim, that is limitations added wholly apart from any need to interpret what the patentee meant by particular words or phrases in the claim." (citation omitted)). The danger of improperly importing a limitation is even greater when the purported limitation is based upon a term not appearing in the claim. "If we once begin to include elements not mentioned in the claim in order to limit such claim . . ., we should never know where to stop." *Johnson Worldwide Assocs., Inc. v. Zebco Corp.*, 175 F.3d 985, 990, 50 USPQ2d 1607, 1610 (Fed. Cir. 1999) (quoting *McCarty v. Lehigh Val. R.R.*, 160 U.S. 110, 116 (1895)).

Amgen's inventive EPO product, according to the disclosure in the '933 patent, is "uniquely characterized by being the product of prokaryotic or eucaryotic host expression (e.g., by bacteria, yeast and mammalian cells in culture) of exogenous DNA sequences obtained by genomic or cDNA cloning or by gene synthesis." '933 patent, col. 10, lines 15-20. In discussing United States Patent No. 4,237,224 (issued to Cohen), the '933 patent defines

"exogenous DNA" by reference as DNA that is foreign to the host organism. *See id.* col. 2, lines 41-47 ("[T]he Cohen et al. patent first involve[s] manufacture of a transformation vector by enzymatically cleaving viral or circular plasmid DNA to form linear DNA strands. Selected foreign ('exogenous' or 'heterologous') DNA strands usually including sequences coding for desired product are prepared in linear form through use of similar enzymes."). During the prosecution of Serial No. 08/468,369, which became the '349 patent, the examiner commented that the application "teaches and enables only cells that have been transformed with exogenous DNA that encodes erythropoietin (EPO) that have the high EPO production required by the claims." TKT asserts, as a result, that its GA-EPO product and process fall outside the scope of the asserted claims because Amgen repeatedly has characterized its claimed products and processes as requiring the use of exogenous EPO DNA, and hence the claims should be limited thereto.

[1] Guided by our principles of claim construction, we agree with the district court that TKT improperly seeks to import the "exogenous" limitation into the claims. The plain meaning of the claims controls here, and they plainly are not so limited. The statement that the invention is "uniquely characterized" by the expression of exogenous DNA sequences does not impel us to accept TKT's position when the asserted claims do not contain such an express limitation. In fact, TKT's position is undermined by the doctrine of claim differentiation, as reference to other claims clearly indicates that Amgen did not intend to limit the invention to the use of exogenous DNA. Unasserted claim 3 of the '933 patent, for example, is virtually identical to claim 1, save for the express limitation regarding the use of "exogenous DNA" (underlined [italicized] portions indicating differences).

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Claim 1##Claim 3

A non-naturally occurring erythropoietin glycoprotein product having the in

 vivo biological activity of causing bone marrow cells to increase production

 of reticulocytes and red blood cells and having glycosylation which differs

 from that of human urinary erythropoietin.##A non-naturally occurring
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glycoprotein product of the expression in a mammalian host cells of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin said product possessing the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having glycosylation which differs from that of human urinary erythropoietin.

Our court has made clear that when a patent claim "does not contain a certain limitation and another claim does, that limitation cannot be read into the former claim in determining either validity or infringement." *SRI Int'l*, 775 F.2d at 1122, 227 USPQ at 586; *see also O.I. Corp. v. Tekmar Co., Inc.*, 115 F.3d 1576, 1582, 42 USPQ2d 1777, 1781 (Fed. Cir. 1997) (expressing the notion that there are practical limits to the doctrine of claim differentiation: "the doctrine cannot alter a definition that is otherwise clear from the claim language, description, and prosecution history."). ***1394** There is a rebuttable presumption that different claims are of different scope. *See Kraft Foods, Inc. v. Int'l Trading Co.*, 203 F.3d 1362, 1366-67, 53 USPQ2d 1814, 1817 (Fed. Cir. 2000); *Multiform Dessicants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1479-80, 45 USPQ2d 1429, 1434 (Fed. Cir. 1998).

The examiner's statement in the prosecution history gives us no pause, as the basis for his rejection was not because transformation with exogenous DNA was not taught, but because "the high EPO production required by the claims" was not. *See* J.A. at 1302 ("The instant application does not guide one of ordinary skill in the art in the discovery of non-transformed vertebrate cells that are capable of the high EPO production recited in the instant claims, [as demonstrated in the reference,] each of which discloses levels of EPO production by vertebrate cells in culture that are far below those levels required in the instant claims."). TKT's position is further undermined because the asserted claims issued. We must presume the examiner did his job, and if he truly thought that the specification taught or enabled only the use of exogenous DNA, the asserted claims would not have issued.

In the end, TKT has not directed our attention to anything in the intrinsic record that rebuts the presumption that the plain meaning of the terms controls. Accordingly, we conclude that the scope of the asserted claims should not be limited to the expression of exogenous DNA.

B

TKT asserts, in addition to the exogenous/endogenous distinction discussed above, that the district court misconstrued the terms "non-naturally occurring," "vertebrate cells," and "mammalian cells" -- which appear in many of the asserted claims -- to include human cells. Reviving the same argument the district court rejected below, TKT contends Amgen expressly disavowed the use of human cells to make human EPO.

The district court found that the definition of the term "non-naturally occurring" can be discerned through the doctrine of claim differentiation. Specifically, the court concluded that TKT's proffered construction must fail in light of '933 patent claim 3, discussed previously, which claims a " *non- naturally occurring* glycoprotein product of the expression in a *mammalian* host cell of an exogenous DNA sequence encoding *human* erythropoietin . . . ." By its terms, then, this claim would cover the expression of human DNA in a cat host cell, for example, because a cat is a mammal. The court thus concluded that the phrase "non-naturally occurring" would be redundant in claim 3 if the phrase had the meaning TKT sought to ascribe to it. Further, because the patent specification compares the biological activity of synthetic products to "EPO isolates from natural sources" or "natural EPO isolates," the court

concluded that non-naturally occurring simply means "not occurring in nature." *Amgen*, 126 F.Supp.2d at 90-91, 57 USPQ2d at 1462-63.

Similarly, finding that the term vertebrate is widely known and understood to cover anything with "a segmented bony or cartilaginous spinal cord [which obviously includes humans]," *id.* at 85, 57 USPQ2d at 1457-58, the court adopted Amgen's proposed construction. The court also adopted Amgen's proposed construction of the term "mammalian cells" appearing in '422 patent claim 1 and '698 patent claim 9 under a similar rationale. *Id.* at 84-86, 57 USPQ2d at 1458.

[2] We indulge a heavy presumption that a claim term carries its ordinary and customary meaning. *CCS Fitness*, 288 F.3d at 1366, 62 USPQ2d at 1662; *see also Gart v. Logitech, Inc.*, 254 F.3d 1334, 1341, 59 USPQ2d 1290, 1295 (Fed. Cir. 2001). Although TKT is correct that the prosecution history is always relevant to claim construction, it is also true that the prosecution history may not be used to infer the intentional narrowing of a claim absent the applicant's clear disavowal of claim coverage, such as an amendment to overcome a rejection. *See York Prods., Inc. v. Central Tractor & Farm Fam. Ctr.*, 99 F.3d 1568, 1575, 40 USPQ2d 1619, 1624 (Fed. Cir. 1996). No such clear disavowal occurred here.

We agree with Amgen that the specification expressly describes humans as a subset of mammals, and mammals, in turn, as a subset of vertebrates. *See* '933 patent, col. 4, lines 47-48; col. 10, line 21. Moreover, the specification can fairly be read to, if not expressly, disclose the use of human DNA in human host cells in culture:

Conspicuously comprehended are expression systems involving vectors of homogeneous ***1395** origins applied to a variety of bacterial, yeast, and mammalian cells in culture as well as to expression systems not involving vectors . . . . *In this regard, it will be understood that expression of, e.g., monkey origin DNA in monkey host cells in culture and human host cells in culture, actually constitute instances of 'exogenous' DNA expression inasmuch as the EPO DNA whose high level expression is sought would not have its origins in the genome of the host.*

'933 patent, col. 37, lines 33-43 (emphasis added). The astute reader will observe what appears to be a breakdown in the parallelism of the sentence emphasized in the block quote above. Specifically, the reference to the expression of "monkey origin DNA in monkey host cells in culture and human host cells in culture" seems a bit nonsensical because the expression of monkey origin DNA in human host cells is perforce the expression of exogenous DNA. The original 1983 application from which all the patents in suit claim priority, by contrast, contained language that upholds the parallelism of the sentence and logically makes sense. It read, in pertinent part: "[I]t will be understood that expression of, e.g., monkey origin DNA in monkey host cells in culture and *human DNA in* human host cells in culture constitute instances of 'exogenous' DNA expression." J.A. at 2862 (emphasis added).

TKT boldly asserts that the variance between the original application and the patents in suit bespeaks some volitional act by Amgen to narrow the scope of the asserted claims in light of certain experimental data. In particular, TKT advances a theory whereby Amgen intentionally removed the language from subsequent applications (allegedly) because test results using human cells were not good, and later admitted (during an opposition proceeding against the European counterpart patent) that the omission was not inadvertent. But the record contains a more benign explanation as to what happened. According to the testimony of Dr. Lin, he was unaware of, and therefore did not authorize, the change. Further, the prosecuting attorney testified in his deposition that to the best of his knowledge the error was a typographical error.

But even assuming that the error was intentional, the district court's claim construction would not be foreclosed: our precedent is clear that claims are not perforce limited to the embodiments disclosed in the specification. *E.g., Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336, 1344, 60 USPQ2d 1851, 1856 (Fed. Cir. 2001) ("[A]n applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention."). Here, the patent plainly discloses the use of human host cells in culture, and our review of the record indicates no "clear disavowal" sufficient to undercut the express disclosure in the specification.

As a result, we are satisfied that the terms "non-naturally occurring," "vertebrate," and "mammalian" should be construed as they were by the district court, in a manner consistent with their plain meaning. Accordingly, we reject TKT's attempt to limit the scope of the asserted claims under an unduly constricted reading of the specification.

C

The final claim construction issue TKT raises is aimed at the district court's alleged failure to discern "source and process" limitations in claims of the '080, '349, and '422 patents. According to TKT, the trial court erred by concluding that the asserted claims are product claims, *i.e.*, that they are directed to a structural entity that is not defined or limited by how it is made. TKT summarily states that this holding must be erroneous because, it asserts, the patentability of the claims depended on the process since "Amgen tried, but failed, to distinguish rEPO from prior art EPOs based on physical differences." We do not agree.

[3] It is telling that neither in the briefing nor at oral argument did TKT direct us to any specific statement in the prosecution history to support the contention that the patentability of the product claims in suit depended upon the process by which those products are obtained. In fact, the original claims of at least one of the patents (the '080 patent) were drafted as product-by-process claims, which claims were cancelled and replaced with "pure" product claims. This is strong evidence that both the patentee and the examiner viewed the claims that ultimately issued as lacking a process component. *See Vanguard Prods., Inc. v. Parker Hannifin Corp.*, 234 F.3d 1370, 1372, 57 USPQ2d 1087, 1089 (Fed. Cir. 2000) ("Parker Hannifin argues that the prosecution history shows that the Vanguard inventors viewed co-extrusion as 'fundamental' to ***1396** manufacture of the claimed gasket, thereby imposing this process of manufacture upon the product claims . . . . However, review of the prosecution history shows that during examination the examiner as well as the applicant treated the product claims as directed to the product itself, and examined the application accordingly.").

In any event, we are not convinced that the source limitations in the asserted claims convert the claims into anything other than product claims. As to the '080 patent, the "non-naturally occurring" limitation in claims 3 and 4 merely prevents Amgen from claiming the human EPO produced in the natural course. By limiting its claims in this way Amgen simply avoids claiming specific subject matter that would be unpatentable under § 101. This court has endorsed this approach, recognizing that patentees can use *negative* limitations such as "non-human" and "non-natural" to avoid rejection under § 101. *See Animal Legal Def. Fund v. Quigg*, 932 F.2d 920, 923, 18 USPQ2d 1677, 1680 (Fed. Cir. 1991). The district court arrived at a similar conclusion, *Amgen*, 126 F.Supp.2d at 89, 57 USPQ2d at 1462-63, and TKT has not demonstrated any error in that conclusion. Similarly, the "not isolated from human urine" limitation in claims 2 and 4 of the '080 patent simply requires that the claimed EPO, however made, be obtained from a source other than human urine. Each of these limitations only excludes human EPO from specific sources and does not restrict the claimed EPO to that produced from any particular source or by any particular method. In sum, claims 2, 3, and 4 of the '080 patent remain broadly drawn to the described "erythropoietin glycoprotein"or "pharmaceutical composition" produced by any method, or obtained from any source, other than those specifically excluded.

As to the '422 patent, the limitation "purified from mammalian cells grown in culture" in claim 1 clearly limits the source of the EPO used in the claimed "pharmaceutical composition." The limitation only speaks to the source of the EPO and does not limit the process by which the EPO is expressed. Rather, the claim is broadly drawn to a "pharmaceutical composition" having certain elements, one of those being EPO "purified from mammalian cells in culture." This reading is in line with the district court's construction and, again, TKT directs us to no error. [FN5]

II

It is axiomatic that claims are construed the same way for both invalidity and infringement. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 842 F.2d 1275, 1279, 6 USPQ2d 1277, 1280 (Fed. Cir. 1988). But because the features of the accused product or

process are often undisputed, this axiom invites a common approach in the appellate arguments by accused infringers: the principal argument challenges the correctness of a trial court's broad claim construction; the contingent argument, assuming the trial court's claim construction is affirmed, challenges validity under 35 U.S.C. § 112 ¶ 1 of the asserted patents in light of that broad construction. *See, e.g., Adv. Cardiovascular Sys. v. Medtronic, Inc.*, 265 F.3d 1294, 60 USPQ2d 1161 (Fed. Cir. 2001); *PPG Indus. v. Guardian Indus. Corp.*, 75 F.3d 1558, 37 USPQ2d 1618 (Fed. Cir. 1996); *Kalman v. Kimberly-Clark Corp.*, 713 F.2d 760, 218 USPQ 781 (Fed. Cir. 1983). TKT employs that approach here. We therefore think it appropriate to address the relevant § 112 issues before turning to the issue of infringement.

Section 112 of the patent statute describes what must be contained in the patent specification. Among other things, it must contain "a written description of the invention, and of the manner and process of making and using it . . . [such] as to enable any person of ordinary skill in the art to which it pertains . . .to make and use the same . . . ." 35 U.S.C. § 112 ¶ 1. Thus, this statutory language mandates satisfaction of two separate and independent requirements: an applicant must both describe the claimed invention adequately and enable its reproduction and use. *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Third, though not in issue here, he must disclose what he considers the best mode of practicing his invention.

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The purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not; the applicant for a patent is therefore required to "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." *Id.* at 1561, 19 USPQ2d at 1115 (citation omitted). Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan. *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997) ("The description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). "Compliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" *Enzo Biochem v. Gen-Probe, Inc.*, 296 F.3d 1316, 1324, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002) (citation omitted). Because of its fact intensive nature, we review a district court's decision on the adequacy of written description for clear error. *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000) (citations omitted).

In addressing TKT's written description arguments, the district court carefully examined whether Amgen's specification adequately described the full breadth of the claims. In the end, the district court rejected TKT's written description challenge, finding that TKT had proven its case only by a preponderance of the evidence -- *not* the clear and convincing standard required as a matter of law. Acknowledging the presence of "a genuine dispute between the expert witnesses," the court weighed the testimony and found that the evidence showed that the descriptions adequately described to those of ordinary skill in the art in 1984 the use of the broad class of available mammalian and vertebrate cells to produce the claimed high levels of human EPO in culture. *Amgen*, 126 F.Supp.2d at 149, 57 USPQ2d at 1507. In so doing, the court credited in particular the testimony of Amgen's expert, Dr. Harvey Lodish, who testified, among other things, that there might be "minor differences" in applying the method of the disclosed examples (utilizing CHO and COS-1 (monkey) cells) to any vertebrate or mammalian cells, but that those of ordinary skill could "easily" figure out those differences in methodology. *Id.*, 57 USPQ2d at 1507.

Much of TKT's argument on appeal challenging this finding dovetails with its claim construction arguments we have already found lacking. For example, TKT asserts that the Amgen patents do not satisfy the written description requirement because: (1) Amgen failed to sufficiently describe the use of all vertebrate and mammalian cells; (2) Amgen deleted use of exogenous human EPO DNA in human cells from its applications; [FN6] (3) Amgen expressly excluded the use of endogenous EPO DNA; (4) Amgen emphasized that the advantage of its invention was "freedom from association with human proteins"; and (5) in using the "uniquely characterized" language to describe

the polypeptides of the invention, Amgen identified exogenous EPO DNA as an essential element of the invention. As a result of these shortcomings, argues TKT, it has clearly and convincingly proven invalidity under *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 45 USPQ2d 1498 (Fed. Cir. 1998), and *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). We are not persuaded that these precedents mandate reversal of the trial court's factual findings as clearly erroneous regarding the written descriptions.

[4] First, in addressing the adequacy of the written description of the '422 patent and with respect to TKT's exogenous DNA arguments, the district court noted:

When the claim is to a composition rather than a process, the written description requirement does not demand that the specification describe technological developments in the way in which the claimed composition is made that may arise after the patent application is filed. *See United States Steel Corp. v. Phillips Petroleum Co.*, 865 F.2d 1247, 1251 [ 9 USPQ2d 1461, 1465 ***1398***In re Koller*, 613 F.2d 819, 824-25 [ 204 USPQ 702, 707 1980); *see also In re Hogan*, 559 F.2d 595, 606 [ 194 USPQ 527, 538 *Reiffin*, 214 F.3d at 1346 [ *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1346, 54 USPQ2d 1915, 1917 *Amgen*, 126 F.Supp.2d at 150, 57 USPQ2d at 1508; *see also id.* at 152, 57 USPQ2d at 1509 (discussing the '080 patent), 154 n.51, 57 USPQ2d at 1510 (discussing the '349 patent). The district court therefore considered TKT's exogenous DNA arguments and, for the reasons stated above, rejected them. On appeal TKT has not argued that its legal analysis was erroneous. Because we have not been directed to any case law to the contrary, we conclude the district court's legal conclusion based on *Phillips Petroleum* was not erroneous and that it properly handled the exogenous DNA issue.

[5] We move now to TKT's argument that Amgen failed to sufficiently describe all vertebrate and mammalian cells as engineered in the claimed invention. We held in *Eli Lilly* that the adequate description of claimed DNA requires a precise definition of the DNA sequence itself -- not merely a recitation of its function or a reference to a potential method for isolating it. 119 F.3d at 1566-67, 43 USPQ2d at 1406 (holding the disclosure of the cDNA sequence of the insulin gene of a rat did not adequately describe the cDNA sequence of the insulin gene of every vertebrate). More recently, in *Enzo Biochem*, we clarified that *Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure. *See Enzo Biochem*, 296 F.3d at 1324, 63 USPQ2d at 1613. Both *Eli Lilly* and *Enzo Biochem* are inapposite to this case because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend. [FN7] Instead, the claims of Amgen's patents refer to types of cells that can be used to produce recombinant human EPO. Thus, TKT can only challenge the adequacy of disclosure of the vertebrate or mammalian host cell -- not the human DNA itself. This difference alone sufficiently distinguishes *Eli Lilly*, because when used, as here, merely to identify types of cells (instead of undescribed, previously unknown DNA sequences), the words "vertebrate" and "mammalian" readily "convey[] distinguishing information concerning [their] identity" such that one of ordinary skill in the art could "visualize or recognize the identity of the members of the genus." *Eli Lilly*, 119 F.3d at 1567, 1568, 43 USPQ2d at 1406. [FN8] Indeed, the district court's reasoned conclusion that the specification's description of producing the claimed EPO in two species of vertebrate or mammalian cells adequately supports claims covering EPO made using the genus vertebrate or mammalian cells, renders *Eli Lilly* listless in this case. *Amgen*, 126 F.Supp.2d at 149, 57 USPQ2d at 1507.

TKT's remaining arguments rely on *Gentry Gallery* . However, we see *Gentry Gallery* as similarly inapt. TKT would have us view *Gentry* as a watershed case, in reliance on an isolated statement -- probably only dicta -- that one of ordinary skill in the art would clearly understand that the location of the reclining controls on the claimed sectional sofa "was not only important, but essential to [the]

invention." 134 F.3d at 1480, 45 USPQ2d at 1503. But as we recently indicated in *Cooper Cameron Corp. v. Kvaerner Oilfield Prods., Inc.*, 291 F.3d 1317, 1323, 62 USPQ2d 1846, 1850-51 (Fed. Cir. 2002), "we did not announce [in *Gentry*] a new 'essential element' test mandating an inquiry into what an inventor ***1399** considers to be essential to his invention and requiring that the claims incorporate those elements." *See also Vas-Cath*, 935 F.2d at 1565, 19 USPQ2d at 1114; *cf. Aro Mfg. Co. v. Convertible Top Replacement Co.*, 365 U.S. 336, 345 (1961) ("[T]here is no legally recognizable or protected 'essential element,' 'gist' or 'heart' of the invention in a combination patent."). Understood in this light, one sees the holding in *Gentry* for what it really was: an application of the settled principle that a broadly drafted claim must be fully supported by the written description and drawings. *See Cooper Cameron*, 291 F.3d at 1323, 62 USPQ2d at 1850-51. After considering extensive testimony from both parties, the district court held this principle met and TKT failed to demonstrate that this analysis was clearly erroneous factually or based on an error of law. *Amgen*, 126 F.Supp.2d at 149-50, 57 USPQ2d at 1507-08.

[6] To the extent the particular facts of *Gentry* are relevant, we also find it distinguishable. First, there is a fundamental difference between Amgen's patented invention and the invention in *Gentry*. In *Gentry* the invention *was* the placement of reclining controls on a central console on a unit of a sectional sofa so as to allow the sofa to have two independent reclining seats face in the same direction (solving a problem present in the prior art). 134 F.3d at 1475, 45 USPQ2d at 1499. The undisclosed element leading to the *Gentry* court's holding of invalidity for lack of an adequate description was a location for the controls other than on the console -- leading to a different and undescribed *product*. *See id.* at 1479, 45 USPQ2d at 1502-03. Amgen's invention is not the location of the control sequences and EPO DNA in relation to the cell, but rather the production of human EPO using those sequences. Thus, the undisclosed element TKT urges invalidates Amgen's product claims is a different *method* (endogenous activation) of making the claimed compositions. But, as the district court noted, under our precedent the patentee need only describe the invention as claimed, and need not describe an unclaimed method of making the claimed product. *Amgen*, 126 F.Supp.2d at 150, 57 USPQ2d at 1507 (citing *Phillips Petroleum*, 865 F.2d at 1251, 9 USPQ2d at 1465; *In re Koller*, 613 F.2d at 824-25, 204 USPQ at 707); *see also Vas-Cath*, 935 F.2d at 1563-64, 19 USPQ2d at 1117. This factual difference alone is sufficient to distinguish this case from *Gentry*.

Second, the statements by the patentee in the written description in this case fall short of what *Gentry* prohibits. The court in *Gentry* concluded that the inventor had clearly expressed in the written description that he considered his invention to be limited to the specific location of the controls on the console on the sofa ("the only possible location") and that any variation was "outside the stated purpose of the invention." *Gentry Gallery*, 134 F.3d at 1479, 45 USPQ2d at 1503. Indeed, in *Gentry* the inventor testified that he only considered locating the controls outside of the console -- and only broadened his application claims accordingly -- after seeing Gentry's competitors introduce products with controls located off the console. *Id.* Here, to be sure, Amgen made statements that its invention is "uniquely characterized" by exogenous expression of DNA. '933 patent col. 10, lines 15-20. When considered in context, however, these statements do not lead to the same conclusion as in *Gentry*. Amgen's statements simply do not clearly indicate that exogenous expression is the *only* possible mode of the invention or that other methods were outside the stated purpose of the invention. Instead, Amgen begins the background section of its written description by stating "[t]he present invention relates generally to the manipulation of genetic materials and, more particularly, to recombinant procedures making possible the production of polypeptides possessing part or all of the primary structural conformation and/or one or more of the biological properties of naturally occurring erythropoietin." '933 Patent, col. 1, lines 18-23. Because of this lack of clear statements by the patentee limiting the claimed invention (and in light of the case law discussed, *ante*), we cannot invalidate a patent for failure to describe a method of producing the claimed compositions that is not itself claimed. Nor could the patentee have described the other method, as it was not developed until 10 years later. We see *Gentry Gallery* as inapplicable in this regard. In light of the evidentiary record and TKT's inability to persuade

us that precedent requires a contrary result, we hold that the district court's finding that Amgen satisfied the ***1400** written description requirement is not clearly erroneous.

B

The enablement requirement is often more indulgent than the written description requirement. The specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without "undue experimentation." *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). Before the district court, TKT bore the burden of clearly and convincingly proving facts showing that the claims were not enabled. *E.g.*, *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1375, 52 USPQ2d 1129, 1141 (Fed. Cir. 1999). Enablement is a question of law; we therefore review the trial court's determination *de novo*, deferring to its assessment of subsidiary facts underlying the legal question unless clearly erroneous. *Bruning v. Hirose*, 161 F.3d 681, 686, 48 USPQ2d 1934, 1939 (Fed. Cir. 1998).

TKT contends that the asserted claims are invalid for lack of enablement. Taking a position that virtually mirrors the written description (and claim construction) arguments previously rejected, TKT posits that the specifications do not enable an ordinarily skilled artisan to practice the full scope of the asserted claims without undue experimentation because they fail to describe the production of EPO using human cells or endogenous human EPO DNA. At bottom, TKT complains that the court erred by failing to follow its findings to their logical conclusion. [FN9]

> [7] But the district court made thorough and complete factual findings supporting its holding that the claims were not proven not enabled, expressly incorporating many of its factual determinations made with respect to written description. As to TKT's endogenous/exogenous arguments, the court concluded the arguments were inapplicable as a matter of law for two reasons. First, "where the method is immaterial to the claim, the enablement inquiry simply does not require the specification to describe technological developments concerning the method by which a patented composition is made that may arise after the patent application is filed." *Amgen*, 126 F.Supp.2d at 160, 57 USPQ2d at 1515 (citing *Phillips Petroleum*, 865 F.2d at 1251, 9 USPQ2d at 1465; *In re Koller*, 613 F.2d at 824-25, 204 USPQ at 707 ; *In re Hogan*, 559 F.2d at 606, 194 USPQ at 538); *see also id.* at 161, 57 USPQ2d at 1516 (discussing the '080 patent), 163-64, 57 USPQ2d at 1518 (discussing the '349 patent). Thus, the specification's failure to disclose the later-developed endogenous activation technology cannot invalidate the patent. *Id.* at 160, 57 USPQ2d at 1516. Second, "the law makes clear that the specification need teach only one mode of making and using a claimed composition." *Id.* at 160, 57 USPQ2d at 1515 (citing *Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1361, 47 USPQ2d 1705, 1719 (Fed. Cir. 1998); *Engel Indus. Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533, 20 USPQ2d 1300, 1304 (Fed. Cir. 1991)); *see also Durel Corp. v. Osram Sylvania Inc.*, 256 F.3d 1298, 1308, 59 USPQ2d 1238, 1244 (Fed. Cir. 2001). This conclusion again makes the specification's failure to disclose TKT's endogenous activation technology legally irrelevant. *Amgen*, 126 F.Supp.2d at 160, 57 USPQ2d at 1515. We reach the same conclusion on appeal, as TKT has not persuaded us that the district court's conclusions in this regard were erroneous.

Focusing specifically on the '422 patent, the enablement inquiry is whether Amgen has enabled all pharmaceutical compositions comprising "a therapeutically effective amount of human erythropoietin," "a pharmaceutically acceptable diluent, adjuvant or carrier," and human erythropoietin "purified from mammalian cells grown in culture." The court found that the specification described and enabled various possible diluents and carriers and provided specific information on effective dosages and therapeutic effect in mice. *Id.* at 148, 57 USPQ2d at 1506. Amgen also described and enabled at least one way of obtaining ***1401** EPO purified from mammalian cells in culture: the genetic manipulation of CHO and COS-1 cells, followed by both described and other well known purification techniques. Finally,

the court accepted testimony indicating that an ordinarily skilled artisan would infer from the COS-1 (monkey) and CHO cell examples that similar outcomes could be expected from other mammalian cells since all mammalian cells produce and secrete hormones like EPO by means of the same fundamental processes. *Id.* at 159, 57 USPQ2d at 1514-15. These are all findings of fact and they have not been shown to be clearly erroneous.

As to the '080 patent, the inquiry is whether Amgen has enabled the production of all EPO glycoproteins having "the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells," "the mature erythropoietin amino acid sequence of FIG. 6," and "[are] not isolated from human urine" or "non-naturally occurring." The court noted that Amgen disclosed the *in vivo* biological effect of EPO upon hematocrit levels in mice and adequately disclosed the sequence of the amino acid residues in figure 6. *Id.* at 151, 57 USPQ2d at 1508-09. Amgen also described and enabled at least one method of producing EPO that was both "non-naturally occurring" and "not isolated from human urine": the genetic manipulation of CHO and COS-1 cells. The court noted with particularity that even TKT's witness, Dr. Kingston, agreed that if one of ordinary skill in the art followed the teachings of Example 10, then such a person could successfully practice the claimed invention. *Id.* at 161, 57 USPQ2d at 1516.

We address the product claims of the '349 patent in more detail, as they differ slightly from the patents we discussed above. The '349 patent claims genetically manipulated "vertebrate cells" -- a composition -- having certain characteristics and properties, including an ability to produce the claimed levels of human EPO. [FN10] The enablement question thus posed is this: having disclosed one way to make the claimed EPO-producing cell, is Amgen entitled to claim all such cells that "can be propagated *in vitro*," comprise "non-human DNA sequences that control transcription," transcribe "DNA encoding human erythropoietin," and produce the claimed amount of EPO? While our precedent does hold that disclosure of one or two species *may* not enable a broad genus, *e.g.*, *In re Vaeck*, 947 F.2d at 495-96, 20 USPQ2d at 1444-45, the district court made several fact-findings indicating that any gaps between the disclosures and the claim breadth could be easily bridged. *See, e.g.*, *Amgen*, 126 F.Supp.2d at 149, 57 USPQ2d at 1514 (crediting Amgen's expert Dr. Lodish's statement that "one of ordinary skill in the art, me, my students, would have understood this not to be limited to the specific types of cells that were used in this example, that other vertebrate cells, mammalian cells, could have been used"); *cf. Enzo Biochem*, 188 F.3d at 1367-68, 1372, 52 USPQ2d at 1133, 1136-37 (affirming nonenablement of claims to anti-sense DNA technology applied to all eukaryotic and prokaryotic organisms because anti-sense was a "highly unpredictable technology" and a "high quantity of experimentation" would be needed to practice the invention outside of the disclosed example); *Vaeck*, 947 F.2d at 495-96, 20 USPQ2d at 1444-45 (holding the examiner did not err in rejecting as nonenabled claims drawn to all genetically-engineered cyanobacteria expressing a given protein because the claimed 150 genera of cyanobacteria represent a vast, diverse, and poorly understood group; heterologous gene expression in cyanobacteria was "unpredictable"; and the patent's disclosure referred to only a genus). The district court found that a skilled artisan could readily have used various cultured vertebrate and mammalian cells to produce human EPO, and this fact was buttressed by numerous post-filing publications that demonstrated the extent of the enabling disclosure. *Amgen*, 126 F.Supp.2d at 162, 57 USPQ2d at 1517 (citing *Gould v. Quigg*, 822 F.2d 1074, 3 USPQ 1302 (Fed. Cir. 1987) for the proposition that an expert may rely on post-filing ***1402** publications to show enablement). The court also found that for those skilled in the art it was a relatively simple matter to determine whether a certain promoter would work within a specific vertebrate cell, whether a particular vertebrate cell would produce human EPO in culture, and whether a particular promoter could be operatively linked to control the transcription of the human EPO DNA. *Id.* In summary, the court once again chose to credit Amgen's witnesses, Drs. Lodish and Wall, on the issue of enablement:

Throughout the testimony of these witnesses, a theme becomes apparent: any challenge which one of ordinary skill in 1984 might have encountered in attempting to make and use the claimed invention using other cultured mammalian cells could be

resolved by experimentation falling short of undue. *Id.* at 159, 57 USPQ2d at 1515.

With these factual findings before us, TKT cannot prevail simply by reasserting in a conclusory manner that Amgen's disclosure does not enable the transformation of all mammalian or vertebrate cells or the production of human EPO. The district court carefully considered these issues, finding in the end that TKT had not met its clear and convincing burden of proof. Finding no clear error in these factual determinations, and having been directed to no legal error committed by the trial court, we will not disturb its holding that the asserted patents are not invalid for failure to meet the enablement requirement of § 112 ¶ 1.

C

Certain concerns are raised by the dissent. My brother in dissent sees the district court as having "abstained from fully inquiring" about compliance with the written description and enablement requirements of § 112, ¶ 1. In light of this strong statement, we write here to highlight what the district court did and did not do in deciding the case below. The district court should be seen as deciding the challenges to validity under each requirement as presented to it by the accused infringer. In doing so, the court fully found the facts that under-girded its conclusions on validity and relied on our case law interpreting and applying § 112. We are largely limited on review to deciding whether those findings based on that testimony are clearly erroneous and we cannot so conclude. We may, of course, review *de novo* the court's interpretation of our precedent.

The dissent, however, does not directly challenge the court's factual findings, nor does it mention the decisions relied on by the district court. Instead, it finds fault in the absence of discussion of other precedents, namely *Eli Lilly*, *Gentry Gallery*, *In re Mayhew*, and *In re Vaeck*, and makes broader arguments seemingly based upon policy considerations.

The dissent would vacate and remand the written description issue because the district court did not cite our precedents *Eli Lilly* and *Gentry Gallery*. According to the dissent, the district court "did not focus on the correct law to be applied" and, for that reason, its "factual findings merit no deference." It is difficult to see how the district court's analysis must be rejected because it did not include discussions of these two decisions or, per the dissent, "the principles they espouse." First, it is far from clear that the defendant based its written description challenge below primarily on these two cases. Second, as we hold above, these cases are simply inapplicable here. Given these considerations, we decline to hold that the failure of the district court to cite these precedents constitutes reversible error.

In addressing the enablement inquiry the dissent looks to two other cases not discussed by the district court. It cites *In re Mayhew*, 527 F.2d 1229, 1233, 188 USPQ 356, 358 (C.C.P.A. 1976), for the proposition that "claims failing to recite a necessary element of the invention fail for lack of an enabling disclosure." There, however, the method claims omitted a step without which the invention as claimed was wholly inoperative (meaning it simply would not work and could not produce the claimed product). *Id.* Here, the lack of a limitation directed to the exogenous expression vector in the product claims is not a failure to describe the structure of the cell or a necessary element of the claimed EPO. Once inside the cell, the transcription control sequence and the human EPO DNA integrate randomly into the host cell chromosomes. The only required description, then, is of the EPO DNA and the transcription control sequences because it is the presence of these sequences in the cell that causes the cell to produce the EPO as claimed. Thus, the lack of ***1403** a description of (or a limitation directed to) the expression vector itself (as separate from the EPO DNA and transcription control sequences) does not render the invention inoperable and therefore does not run afoul of *In re Mayhew*, 527 F.2d at 1233, 188 USPQ at 358 (affirming examiner's rejection of claims not limited to having a cooling zone at the exit of a steel strip from a zinc bath because the specification indicated that without that cooling bath the invented process would not work).

The dissent's reliance on *In re Vaeck* is also misplaced. *Vaeck* is cited for the proposition that the disclosure of one or two species (here monkey and hamster cells) "may not enable a broad genus under the circumstances." 947 F.2d at 496, 20

USPQ2d at 1444-45. But then again, it may; the inquiry is fact- specific. Here the district court held the disclosure did enable the genus because the differences between using the two described mammalian (and vertebrate) cells and other such cells were small and easily accommodated by the artisan. Thus, in assessing the evidence, the court found that the defendant's evidence fell short of clear and convincing.

But more fundamentally, we think the dissent unfairly characterizes the district court's careful and reasoned handling of the § 112 issues. The dissent repeatedly suggests that the district court "simply refused" to consider whether, having disclosed only one means to make EPO produced by vertebrate or mammalian cells, Amgen was entitled to claims for all such cells and EPO. Specifically, the dissent asserts that the district court "abstained" from considering whether the absence of a claim limitation on the means of expression raises § 112 issues. [FN11] We find this hard to understand. The district court explicitly analyzed these requirements in addressing defendant's specific challenges to validity. It decided they were not proven sufficiently and its decision is supported both by citations to our precedent and its own factual findings. Thus, rather than refusing to answer the § 112 questions, it seems the district court did answer them affirmatively.

In addressing this specific issue, the district court relied principally on two of our precedents: *Phillips Petroleum* and *Cellpro*. The court construed the former as not requiring the written description to include later- developed methods for making a claimed product. *Amgen*, 126 F.Supp.2d at 150, 160, 57 USPQ2d at 1508, 1515. The court construed the latter as holding that a product claim is supported by adequate written description and enabling disclosure even if it describes only one method of making the claimed product. *Id.* at 160, 57 USPQ2d at 1515. These cases have not been shown to be incorrectly applied by the district court. And we, like the district court, are obligated to follow them both, as they explicitly support the court's rulings. *Phillips Petroleum*, 865 F.2d at 1251, 9 USPQ2d at 1465 (holding that the patentee was entitled to a prior filing date because the earlier disclosure of polypropylene as known at that time described and enabled a later claim to "[n]ormally solid polypropylene" even though a new, higher molecular weight form of polypropylene had been subsequently discovered), and *Cellpro*, 152 F.3d at 1361, 47 USPQ2d at 1719 (affirming summary judgment of enablement of a product claim over a challenge that two alternative embodiments disclosed in the patent were not enabled because "the enablement requirement is met if the description enables any mode of making and using the invention").

Rather than addressing these precedents, the dissent makes broad arguments that are not specifically grounded in our precedent. The dissent asks whether Amgen's disclosure "entitles it to claim *all* EPO produced by mammalian cells in culture, or *all* cultured vertebrate cells that produce EPO." (emphasis in original). While this broad entitlement question may be important as a policy matter, where, as here, we have applicable precedents, we are bound by the specific inquiries they mandate. Here, we, as did the district court, look to the requirements of § 112 as interpreted by our precedent. In short, the district court cannot have committed legal error by faithfully following controlling precedent of this court.

Lastly, the dissent emphasizes that omissions in the claim limitations and in the disclosures of the specifications "raised enablement issues." If the claims were still in prosecution ***1404** before the PTO, perhaps the examiner could make an issue of such omissions. The dissent talks of what is "essential for the *patentability* of the claims." (emphasis added). But the question here is not patentability of application claims, but validity of issued claims that are presumed valid by statute. Now a heavy burden falls on the challenger. The district court found that the challenger had not carried that burden. It admitted that the questions were close -- indeed, it found invalidity proven, but only by a preponderance. Hence, rather than refusing to decide questions of validity under § 112, it did decide them under the proper standard of proof. We see no reversible error.

III

Having addressed the claim interpretation and § 112 issues, we move to the second step of the infringement analysis: comparison of the properly construed claims to the accused product or process.

*See, e.g., CCS Fitness*, 288 F.3d at 1365, 62 USPQ2d at 1662. Our review of this step differs depending upon whether the issue of infringement was resolved on summary judgment or after a full trial. *See Cole v. Kimberly-Clark Corp.*, 102 F.3d 524, 528, 41 USPQ2d 1001, 1004 (Fed. Cir. 1996). In the case of summary judgment, as with claim 1 of the '422 patent, we review *de novo* the trial court's finding that there was no genuine issue as to any material fact regarding infringement. *Id.*, 41 USPQ2d at 1004; Fed. R. Civ. P. 56(c). After a full bench trial, infringement is a question of fact that we review, of course, for clear error. *Ultra-Tex Surfaces, Inc. v. Hill Bros. Chem. Co.*, 204 F.3d 1360, 1363, 53 USPQ2d 1892, 1895 (Fed. Cir. 2000). When JMOL is entered under Fed. R. Civ. P. 52(c), as with the '698 and '080 patents, we review the district court's determination for clear error, as if it had been entered at the close of all the evidence. *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343, 56 USPQ2d 1641, 1643 (Fed. Cir. 2000). Anchored in the proper scope of review for each claim in dispute, we now address the trial court's infringement analysis.

A. The '933 Patent

Amgen asserted the following three claims of the '933 patent against TKT:

1. A non-naturally occurring erythropoietin glycoprotein product having the *in vivo* biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells and having glycosylation which differs from that of human urinary erythropoietin.

2. The non-naturally occurring EPO glycoprotein product according to claim 1 wherein said product has a higher molecular weight than human urinary EPO as measured by SDS-PAGE.

9. A pharmaceutical composition comprising an effective amount of a glycoprotein product effective for erythropoietin therapy according to claim 1, 2, 3, 4, 5, or 6 and a pharmaceutically acceptable diluent, adjuvant or carrier.

Critical for our purposes is the final limitation of claim 1, which states that the claimed glycoprotein has "glycosylation which differs from that of human urinary erythropoietin." Glycosylation is the addition of carbohydrate side chains to amino acid residues in protein sequences to form glycoproteins. *Encyclopedia of Molecular Biology* at 1047. At the *Markman* hearing, Amgen asserted that the phrase meant "the attached carbohydrate groups differ when analyzed by standard prior art techniques known as of 1983-84." TKT argued, by contrast, that it meant "the carbohydrate groups attached to side chains of the erythropoietin polypeptide backbone differ by Western blot analysis and SDS/PAGE and carbohydrate composition analysis from those of human urinary erythropoietin to at least the degree described in the patents-in-suit."

Thus, the primary difference concerned which, if any, techniques were acceptable to determine whether the glycosylation was different. The district court found that the examples in the specification teach three measurement methods, but that they failed to limit "glycosylation which differs" to those methods. The court ruled, therefore, that the phrase means: "Glycosylation as to which there is a detectable difference based upon what was known in 1983- 1984 from that of human urinary erythropoietin, having in mind that the patent holder, Amgen, taught the use of this Western blot, SDS-PAGE and monosaccharide test." *Amgen*, 126 F.Supp.2d at 91-92, 57 USPQ2d at 1463.

***1405** It is undisputed that in 1983, there were at least two analytical techniques available for detecting differences in glycosylation between two glycoproteins. SDS-PAGE is a type of gel electrophoresis in which the glycoprotein of interest is bound to a charged compound that denatures the glycoprotein, which in turn is subjected to an electric field; glycoproteins of different molecular weight (reflecting their different glycosylations) will migrate through the electric field at different speeds. *Id.* at 124, 57 USPQ2d at 1488. Isoelectric focusing ("IEF"), a second technique known to artisans in 1983, is similar to SDS-PAGE except that it determines the pH at which a protein is electrically neutral because the charge is placed in the gel in the form of a pH gradient, rather than on the glycoprotein itself. *Id.* at 125, 57 USPQ2d at 1488. The data obtained by both these methods can be visualized by Western blot, allowing an approximation of the molecular weight.

There was little dispute that any of these tests could be used to determine the glycosylation of a

glycoprotein. Indeed, the district court noted that the testimony of an Amgen witness, Dr. Cummings, "would discharge Amgen's duty of showing by a preponderance of the evidence that HMR4396 has glycosylation which differs from that of human urinary EPO." *Id.* at 127, 57 USPQ2d at 1490. However, the court also credited evidence that indicated two uEPO preparations produced from the same batch of starting materials could nevertheless have different glycosylation patterns. *Id.* at 129, 57 USPQ2d at 1492 ("[A] skilled artisan in 1984 would have understood that urinary erythropoietin samples obtained using different purification methods could have different glycosylation. As a result, the glycosylation of human urinary erythropoietin was in 1984, and continues to be, a moving target."). Consequently, because the district court concluded that the patent failed to identify a single standard by which the "difference" could be measured, it held that TKT did not infringe and the '933 patent was invalid for failure to satisfy 35 U.S.C. § 112:

> The claim language of the '933 patent, however, presupposes that the glycosylation of urinary erythropoietin is a fixed, identifiable marker against which the glycosylation of recombinant EPOs can be measured. Yet, how can one prove that a recombinant EPO has glycosylation which differs from that of urinary EPO when the glycosylation of urinary EPO itself varies? The Court need not answer this conundrum. All that need be said is that Amgen's showing that GA-EPO has glycosylation which differs from but one of the many heterogeneous urinary EPOs is insufficient to carry its burden of proving infringement by a preponderance of the evidence that TKT infringes the claim limitation. *Id.* at 129, 57 USPQ2d at 1492.

Amgen argues on appeal that an ordinarily skilled artisan in 1984 would have understood, based upon the patent disclosure, that there were two principal processes for purifying uEPO, with the technique taught by Miyake (SDS-PAGE) recognized as the standard. It asserts that it carried its burden of proving infringement because its empirical evidence "unequivocally demonstrated the glycosylation difference between Miyake-purified uEPO and the accused product." But it seems to us that Amgen has failed to address the trenchant question on this issue, *i.e.*, whether uEPO is necessarily glycosylated in the same way. Amgen deals rather cavalierly with the question in both its principal and reply brief, stating summarily that the district court erred and suggesting that the question is unimportant.

> [8] By definition, one must know what the glycosylation of uEPO is with certainty before one can determine whether the claimed glycoprotein has a glycosylation different from that of uEPO. In its discussion characterizing recombinant glycoprotein products, the specification of the '933 patent does not direct those of ordinary skill in the art to a standard by which the appropriate comparison can be made. *See* '933 patent, col. 28, line 33 - col. 29, line 7. The district court considered evidence that experiments conducted by Amgen in 1984 showed that different urinary EPO preparations had different glycosylation. For example, EPO purified from the urine of a single patient ("Lot 82") using a modified Miyake procedure was shown to have a different glycosylation from other human uEPO (taken from Goldwasser). *Amgen*, 126 F.Supp.2d at 129, 57 USPQ2d at 1491-92. And so, even assuming that Amgen is correct that one of ordinary skill in the art would have understood the benchmark test for glycosylation ***1406** to be Miyake, its contention still fails. As the district court noted, the Miyake article provides a method of purification, but hardly suggests uniformity of glycosylation of the human uEPO studied:
>
> The 1977 Miyake et al. publication, for example, describes the purification from the same starting material of two homogeneous urinary EPO preparations (Fraction II and Fraction IIIA) that had about the same potency in terms of biological activity. Fractions II and IIIA . . . had different carbohydrate compositions and, therefore, differed from each other in glycosylation. Thus, these two uEPO preparations, though produced by the same procedure (*Miyake) and derived from the same batch of starting material, nonetheless had different glycosylation. *Id.* at 129, 57 USPQ2d at 1491; *see also* Miyake, *Purification of Human Erythropoietin* , J. Bio. Chem. 5558, 5562 (1977) ("In spite of our finding of similar potency and molecular size, these two preparations [Fractions II and IIIA] must be considered different. The chemical basis for this difference is now being studied."). Amgen fails to controvert or otherwise address this evidence in its cross-appeal.

Under 35 U.S.C. § 112 ¶ 2, a patent applicant is required, at the close of his specification, to "particularly point[] out and distinctly claim[] the subject matter the applicant regards as his invention." The requirement of claim definiteness set out in § 112 ¶ 2 assures that claims in a patent are "sufficiently precise to permit a potential competitor to determine whether or not he is infringing." *Morton Int'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470, 28 USPQ2d 1190, 1195 (Fed. Cir. 1993). The standard of indefiniteness is somewhat high; a claim is not indefinite merely because its scope is not ascertainable from the face of the claims. *Cf., e.g., LNP Eng'g Plastics, Inc. v. Miller Waste Mills, Inc.*, 275 F.3d 1347, 1359-60, 61 USPQ2d 1193, 1202 (Fed. Cir. 2001) (affirming district court finding that patent was not indefinite, despite testimony from a co-inventor that he did not understand what the claim limitation "substantially completely wetted" meant). Rather, a claim is indefinite under § 112 ¶ 2 if it is "insolubly ambiguous, and no narrowing construction can properly be adopted." *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1375, 60 USPQ2d 1272, 1276 (Fed. Cir. 2001); *Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1349, 63 USPQ2d 1769, 1776 (Fed. Cir. 2002) ("It is not our function to rewrite [indefinite] claims to preserve their validity."). Applying these legal maxims to the facts of this case, we agree with the district court that the claims requiring "glycosylation which differs" are invalid for indefiniteness.

We find erroneous, however, its conclusion that invalidity for indefiniteness should be found only in the alternative. A claim is indefinite if, when read in light of the specification, it does not reasonably apprise those skilled in the art of the scope of the invention. *See Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1378, 55 UPQ2d 1279, 1282 (Fed. Cir. 2000) (citing *Personalized Media Comm., LLC v. ITC*, 161 F.3d 696, 705, 48 USPQ2d 1880, 1888 (Fed. Cir. 1998)). So it is here. Recognizing that it was faced with a "conundrum" regarding claim construction, the court held that the patent was not infringed because Amgen could not meet its burden simply by showing "that GA-EPO has glycosylation which differs from but one of the many heterogeneous urinary EPOs." *Amgen*, 126 F.Supp.2d at 129, 57 USPQ2d at 1492. That the court recognized that one of ordinary skill in the art would have been faced with this "conundrum" should have ended the inquiry, for such ambiguity in claim scope is at the heart of the definiteness requirement of 35 U.S.C. § 112 ¶ 2. One cannot logically determine whether an accused product comes within the bounds of a claim of unascertainable scope. Accordingly, the finding that TKT does not infringe the '933 patent is vacated and the finding that the '933 patent is invalid under § 112 is affirmed.

B. *The '080 Patent*

Claims 2-4 of the '080 patent are at issue:

2. An isolated erythropoietin glycoprotein having the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6 and is not isolated from human urine.

3. A non-naturally occurring erythropoietin glycoprotein having the in vivo biological ***1407** activity of causing bone marrow cells to increase production of reticulocytes and red blood cells, wherein said erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6.

4. A pharmaceutical composition comprising a therapeutically effective amount of an erythropoietin glycoprotein product according to claim 1, 2, or 3.

The critical limitation of the asserted claims in the '080 patent is the requirement that the erythropoietin glycoprotein "comprise[] the mature erythropoietin amino acid sequence of Fig. 6." The court construed the claim term "mature erythropoietin amino acid sequence of Figure 6" that appears in claims 4 and 6 of the '698 patent and claims 2 and 4 of the '080 patent. The dispute here arises out of a mistake in the specification. At the time the patent was drafted, it was believed that the sequence included 166 amino acids, and this belief is depicted in Figure 6. In fact, later research demonstrated that the full sequence was actually *165* amino acids; the last (arginine) is actually cleaved off prior to the protein's secretion from the cell. Amgen argued that the reference to Figure 6 was irrelevant, even if the figure had too many amino acids, because it still

showed the "mature [i.e., 165] erythropoietin amino acid sequence." TKT argued that the reference to Figure 6 required the term to be construed as depicted in Figure 6, and thus with 166 amino acids. Following trial, [FN12] the court adopted TKT's proposal, relying on what it considered key language in the specification supporting that construction: "Fig. 6 thus serves to identify the primary structural conformation (amino acid) sequence of mature human EPO as including 166 specified amino acid residues . . . ." '080 patent, col. 12, lines 3-5. *Amgen*, 126 F.Supp.2d at 86-87, 57 USPQ2d at 1459.

In total, Figure 6 consists of five separate figures denominated Figs. 6A through 6E, which collectively disclose the sequence of human genomic EPO DNA and the encoded EPO. The detailed description in the '080 patent indicates that the specificity of Figure 6 is not to be lightly disregarded:

Fig. 6 thus serves to identify the primary structural conformation (amino acid sequences) of mature human EPO as including 166 specified amino acid residues (estimate M.W.=18,399). Also revealed in the Figure is the DNA sequence coding for a 27 residue leader sequence along with 5' and 3' DNA sequences which may be significant to promoter/operator functions of the human gene operon. Sites for potential glycosylation of the mature human EPO polypeptide are designated in the Figure by asterisks. It is worthy of note that the specific amino acid sequence of Fig. 6 likely constitutes that of a naturally occurring allelic form of human erythropoietin. Support for this position is found in the results of continued efforts at sequencing of urinary isolates of human erythropoietin which provided the finding that a significant number of erythropoietin molecules therein have a methionine at residue 126 as opposed to a serine as shown in the Figure.

'080 patent, col. 21, lines 29-40.

When the district court revisited the "Figure 6" issue, it concluded that the language of the claims, read in conjunction with the portion of the specification excerpted above, clearly identified the mature erythropoietin amino acid sequence as exactly depicted in Figure 6. In so doing, the court expressly rejected Amgen's contention that the claim should be read as covering the mature amino acid sequence, of erythropoietin, whatever its number of amino acids. *Amgen*, 126 F.Supp.2d at 100, 57 USPQ2d at 1470 ("Had Amgen claimed only 'the mature erythropoietin amino acid sequence' without associating or linking that amino acid sequence to Figure 6 its argument that its claims cover whatever sequence (whether it contained 165 or 166 amino acids) is ultimately secreted by the cell might have more momentum."). The district court therefore found at the close of Amgen's case that HMR4396 does not literally infringe the asserted claims of the '080 patent.

The issue of infringement under the doctrine of equivalents was much closer, and likewise centered on the "Figure 6" limitation. [FN13] ***1408** The district court concluded that Amgen had proven by a preponderance of the evidence that the 165 amino acid sequence satisfied the function-way-result test, crediting in particular the testimony of Dr. Lodish that TKT's missing arginine residue (the 166th amino acid appearing in Figure 6) does not affect the *in vivo* biological activity of its EPO product. *Id.* at 133, 57 USPQ2d at 1495. In reaching its conclusion, the court rejected TKT's argument that Amgen was not entitled to any range of equivalents under *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki*, 234 F.3d 558, 566, 56 USPQ2d 1865, 1870 (Fed. Cir. 2000), because during prosecution it had narrowed the scope of the claim for reasons related to patentability. The parties have cross-appealed on this patent, with Amgen asserting that the district court erred by finding no literal infringement and TKT continuing to press its estoppel theory as a basis for denying any range of equivalents.

Naturally, Amgen continues to focus on the "mature" portion of the relevant claim limitations to support its argument that the trial court erred by finding no literal infringement. According to Amgen, the practical result of the trial court's conclusion is to read out from the claims the preferred embodiment of the invention because the specification makes clear that "mature" human EPO is that form which circulates in the blood, *i.e.*, the 165 amino acid form that has already been secreted. This argument strains reason to its breaking point; our reading of the patent, like the district court's, will support no such interpretation.

[9] Amgen's argument is based upon a misconstruction of the term "including" that evinces a misunderstanding of the plain meaning of that term, as well as the term "comprise," which appears in the '080 patent claims. [FN14] "Comprising is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1633 (Fed. Cir. 1997). The word "include" means the same thing. *See Hewlett-Packard Co. v. Repeat-O-Type Stencil Mfg. Corp., Inc.*, 123 F.3d 1445, 1451, 43 USPQ2d 1650, 1655 (Fed. Cir. 1997) ("The claim term 'including' is synonymous with 'comprising,' thereby permitting the inclusion of unnamed components."); *see also Webster's II New Riverside University Dictionary* 619 (1984) (" *include*: 1. To have or take in as a part or member: CONTAIN; 2. To put into a group class, or total."). Thus, a claim reciting "a widget comprising A and B," for example, would be infringed by any widget containing A and B, no matter that C, D, or E might be present.

If, then, as the specification states, "the primary structural conformation (amino acid sequence) of mature human EPO as including 166 specified amino acid residues," it is simply illogical for Amgen to argue that that means anything other than, at minimum, the 166 amino acids shown in Figure 6. This is verified by the fact that '080 claims 2 and 3 claim an erythropoietin glycoprotein " *compris[ing]* the mature erythropoietin amino acid sequence of Fig. 6 . . . ." Again, read properly in light of the term "comprising," this means that the claimed glycoprotein must have -- at minimum -- all 166 amino acids shown in Figure 6.

Turning to the finding of infringement under the doctrine of equivalents, TKT asserts that Amgen should be estopped from obtaining such coverage under *Festo*. Specifically, TKT alleges that the "mature amino acid sequence of Figure 6" limitation that appears in the '080 patent was added to overcome a double-patenting rejection, and therefore constitutes an amendment related to patentability. We agree.

The district court correctly found that the amendment, although voluntary, was made to avoid a "same invention" double patenting rejection, *Amgen*, 126 F.Supp.2d at 135, 57 USPQ2d at 1496, and although the Supreme Court reversed our decision in *Festo* and rejected the notion of an absolute bar to the doctrine of equivalents, it agreed with our holding "that a narrowing amendment to satisfy any requirement of the Patent Act may give ***1409** rise to an estoppel." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki*, 535 U.S. 722, 122 S. Ct. 1831, 1839 (2002). Contrary to the district court's conclusion, "'[s]ame invention' double patenting is based upon 35 U.S.C. § 101, which states that an inventor may obtain ' *a* patent' for an invention." *In re Lonardo*, 119 F.3d 960, 965, 43 USPQ2d 1262, 1266 (Fed. Cir. 1997) (emphasis added). Therefore, the district court's finding of equivalent infringement of the '080 patent is vacated and remanded for an analysis under the narrow ways of rebutting the Supreme Court's presumption of estoppel. *Festo*, 122 S. Ct. at 1839.

C. The '698 Patent

The '698 patent is directed generally to a process for producing a glycosylated erythropoietin polypeptide. Claims 4-9 are at issue. Independent claims 4 and 6 read as follows:

4. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps:

a) growing, under suitable nutrient conditions, vertebrate cells comprising promoter DNA, other than human erythropoietin promoter DNA, operatively linked to DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and

b) isolating said glycosylated erythropoietin polypeptide expressed by said cells

6. A process for the production of a glycosylated erythropoietin polypeptide having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells comprising the steps of:

a) growing, under suitable nutrient conditions, vertebrate cells comprising amplified DNA

encoding the mature erythropoietin amino acid sequence of FIG. 6; and

b) isolating said glycosylated erythropoietin polypeptide expressed by said cells.

Infringement of dependent claims 5 and 7-9 rises or falls with the analysis that applies to independent claims 4 and 6. [FN15] The phrase "operatively linked" appears in claim 4 of the '698 patent, and is related by dependency to claims 5 and 9. According to the district court, the phrase relates to the relationship between promoter DNA and the DNA that is transcribed downstream from the promoter DNA. Amgen contended that the phrase means "positioned such that it provides for initiation of transcription of a gene." TKT argued that the term means positioned adjacent "to the DNA encoding EPO in a way that maintains the capability to initiate transcription of EPO DNA." In other words, Amgen argued that the words "operatively linked" imposed no spatial restriction, whereas TKT contended that because the patent allegedly taught placing the promoter DNA immediately adjacent to the DNA encoding EPO, the term "operatively linked" ought be limited by location. The district court held that the term "operatively linked" means "the promoter DNA is linked to the EPO DNA is such a way that maintains the capability of the promoter DNA to initiate transcription of the EPO DNA." *Amgen*, 126 F.Supp.2d at 90, 57 USPQ2d at 1462.

The district court granted TKT summary judgment of non-infringement of independent claims 4 and 6 (and hence dependent claims 5 and 7-9) of the '698 patent because it found that Amgen had failed to carry its Rule 52(c) burden. *Id.* at 102, 57 USPQ2d at 1471. Amgen assails this conclusion as not in accordance with law, inasmuch as the differences considered dispositive by the district court are not claimed and thus have no bearing on a proper infringement analysis. In fact, according to Amgen, the district court neglected to identify any limitation of the '698 patent that the accused process fails to literally meet, and also failed to explain why, in the absence of literal infringement, those limitations were not otherwise equivalently met. We agree with Amgen, and therefore conclude *vacatur* is appropriate.

The district court properly recognized that the infringement analysis of process claims is necessarily different from that for product claims. *See id.* at 102, 57 USPQ2d at 1471 ("The process patent gives notice to competitors that the steps described therein are not to be repeated to achieve the same result. Thus, whereas in the product patent context, differences in process are meaningless, here, in the process patent context, these differences mean everything."). But after a correct discussion of the differences in the infringement analysis, the court eschewed the cardinal principle that the accused device must be compared to the claims rather than to a preferred or commercial embodiment. *Id.* ("Based on . . . *the many differences between Amgen's and TKT's processes* . . . Amgen's proof of infringement on the '698 patent [is] insufficient . . . .") (emphasis added).[10] The district court properly recognized that the infringement analysis of process claims is necessarily different from that for product claims. *See id.* at 102, 57 USPQ2d at 1471 ("The process patent gives notice to competitors that the steps described therein are not to be repeated to achieve the same result. Thus, whereas in the product patent context, differences in process are meaningless, here, in the process patent context, these differences mean everything."). But after a correct discussion of the differences in the infringement analysis, the court eschewed the cardinal principle that the accused device must be compared to the claims rather than to a preferred or commercial embodiment. *Id.* ("Based on . . . *the many differences between Amgen's and TKT's processes* . . . Amgen's proof of infringement on the '698 patent [is] insufficient . . . .") (emphasis added).

For example, the court concluded that a fundamental distinction between the respective processes was that TKT employs homologous rather than heterologous recombination, whereas "[i]n order to make EPOGEN®, Amgen transfects [CHO] cells with a vector that contains both viral promoter DNA and the human EPO gene." *Id.* This clear reference to the preferred embodiment of Example 10, which the district court considered "the process most heavily relied upon by Amgen in its patent," *id.* at 103, 57 USPQ2d at 1472, misses the point that none of the claims at issue contain such a limitation. And apart from the limitations of the asserted claims, the differences in the two processes are wholly irrelevant to the infringement

analysis.

The district court likewise found material the fact that TKT places its promoter and enhancer farther upstream than does Amgen. In light of the court's claim construction, however, it would seem TKT satisfies the "operatively linked" limitation, as there is no question that TKT's promoter causes its intended functional effect. In any event, the trial court once again compared the accused process by reference to an example rather than the *claimed* process:

As explained in Example 7 and illustrated in Figure 4, Amgen created the vector by cleaving, with BstEII restriction endonucelases . . . 'at a position which is 44 base pairs 5' to the initiating ATG coding for the pre- peptide and approximately 680 base pairs 3' to the HindIII restriction site' . . . . TKT's process has within the DNA sequence upstream of the codons that express the EPO polypeptide several ATG sites . . . . The court finds that such a process is sufficiently different from that encompassed by Amgen's invention that judgment of non-infringement should follow. *Id.*

Again, this was legal error insofar as the infringement analysis is not tied to the asserted claims. We therefore vacate and remand so that the court may conduct a proper infringement inquiry in the first instance, comparing the accused device to the properly construed claims without limiting their scope to the examples in the specification or other limitations that are not properly a part of claims 4-9.

D. *The '422 Patent*

Claim 1 of the '422 patent, the only one in dispute, claims "[a] pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is purified from mammalian cells grown in culture." In the *Markman* hearing, Amgen contended the phrase "purified from mammalian cells grown in culture" meant "purified from the in vitro culture in which the mammalian cells have been grown," whereas TKT argued that it meant "obtained in a substantially homogeneous state from the mammalian cells in which it was produced and not from the cell culture media." Concluding that TKT's construction would exclude the patent's preferred embodiment (Example 10), the court read the phrase "mammalian cells grown in culture" as a whole to encompass purification techniques from the cells *or* the cell culture medium. *Id.* at 88-89, 57 USPQ2d at 1460-61. As indicated earlier, the district court immediately turned to and granted Amgen's motion for summary judgment of infringement of the '422 patent at the close of the *Markman* hearing.

According to the district court, it was clear from the beginning that the accused product met most limitations of claim 1. That HMR4396 was a pharmaceutical composition that contained a therapeutically effective amount of human erythropoietin was plain, in view of the Investigational New Drug Application ***1411** ("INDA") that TKT filed with the Food and Drug Administration. *Id.* at 94-95, 57 USPQ2d at 1465. The district court further concluded that HRM4396 contained "a pharmaceutically acceptable diluent, adjuvant or carrier" in view of the testimony of TKT's Rule 30(b)(6) designee, who testified that the HRM4396 recovered in bulk from the culturing of human cells was diluted with a phosphate buffer to control the pH and provide a product of desired strength. *See id.* at 95, 57 USPQ2d at 1466. The sole remaining issue, then, was whether the accused product was "purified from mammalian cells grown in culture." Rather than taking the utterly untenable position that humans are not mammals, TKT conceded infringement under the court's claim construction. *Id.* at 95, 57 USPQ2d at 1466.

TKT tries three different tactics on appeal to escape this concession of infringement. First, TKT argues that "mammalian cells," as the phrase is used in the '422 patent, do not include its cells because Amgen excluded the use of human cells to produce human EPO from its invention. Second, TKT asserts that the finding of infringement was in error because the patent specification defines pharmaceutical compositions "as comprising 'polypeptides of the invention'," and HRM4396 is not a "polypeptide of the invention" inasmuch as the invention is "uniquely characterized" by (and hence limited to) exogenous EPO DNA. Finally, TKT challenges the finding of infringement because, it asserts, the intrinsic evidence limits the phrase "purified from mammalian cells grown in culture" to purification that takes place inside the cells, and

not -- like TKT -- from the culture media. [FN16] As infringement of the '422 patent was granted on summary judgment, we review the district court's conclusion *de novo*, applying the same standard applied by the trial court. *Schering Corp. v. Amgen, Inc.*, 222 F.3d 1347, 1351, 55 USPQ2d 1650, 1653 (Fed. Cir. 2000). Under this standard, we agree with the trial court that a grant of summary judgment of infringement of the '422 patent was warranted.

We cannot accept, for the reasons already stated, TKT's proposed reading of the claim term "mammalian" and its attempt to import the term exogenous into the claims; we therefore reject out of hand the contention that Amgen expressly excluded the use of human cells to express EPO and the use of endogenous DNA from the scope of its invention. Thus, the issue resolves to a narrow one: the accused product, HRM4396, infringes '422 patent claim 1 unless TKT is correct that the claim limitation "purified from mammalian cells grown in culture" means that the EPO product must be recovered directly from the cell, and not from the culture medium.

At the *Markman* hearing, Amgen contended the phrase means "purified from the in vitro culture in which the mammalian cells have been grown"; TKT argued that it means "obtained in a substantially homogeneous state from the mammalian cells in which it was produced and not from the cell culture media." The trial court read the phrase to encompass purification techniques from the cells *or* the cell culture medium because to do otherwise, it found, would exclude the patent's preferred embodiment as disclosed in Example 10. *Amgen*, 126 F.Supp 2d at 88-89, 57 USPQ2d at 1461.

[11] Example 10 "describes expression systems employing Chinese hamster ovary (CHO) DHFR cells and the selectable marker, DHFR." '422 patent, col. 25, lines 38-40. As a part of the description, the example discloses that gene amplification in cell culture media is possible to increase productivity of the targeted recombinant EPO product. After describing an example of such a gene amplification system, the specification goes on to state: "The productivity of the EPO producing CHO cell lines described above can be improved by appropriate cell culture techniques. The propagation of mammalian cells in culture generally requires the presence of serum in the growth media. *A method for production of erythropoietin from CHO cells in media that does not contain serum greatly facilitates the purification of erythropoietin from the culture media.*" *Id.*, col. 27, lines 8-14 (emphasis added). We agree with the district court that this disclosure -- the undisputed preferred embodiment of the invention -- contemplates purification of erythropoietin from the culture media. *See also* '933 patent, col. 28, lines ***1412** 28-32 ("Mammalian cell expression products may be readily recovered *in substantially purified form from culture media* using HPLC (C4) employing an ethanol gradient, preferably at pH7." (emphasis added)).

TKT does not challenge the district court's conclusion regarding the disclosure of Example 10. Accordingly, TKT's challenge ultimately must fail unless we read the preferred embodiment out of the claims, but rare is the case where we should or will do so. A claim interpretation that reads out a preferred embodiment "is rarely, if ever, correct and would require highly persuasive evidentiary support." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583, 39 USPQ2d 1573, 1578 (Fed. Cir. 1996). We have done so only one time -- in an instance where the patent applicant limited the full scope of the claim language to omit the preferred (and only disclosed) embodiment in order to overcome an examiner's rejection. *See Elektra Instr. S.A. v. O.U.R. Scientific Int'l, Inc.*, 214 F.3d 1302, 1308, 54 USPQ2d 1910, 1914 (Fed. Cir. 2000). The present case lacks the "persuasive evidentiary support" necessary for us to read the claims so as to exclude the preferred embodiment disclosed in Example 10; we therefore decline to do so.

E. The '349 Patent

The '349 patent contains one method claim and six product claims that are drawn generally to types of vertebrate cells grown in culture. At issue are claims 1, 3-4, and 6-7:

1. Vertebrate cells which can be propagated in vitro and which are capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100 U of erythropoietin per 10 6cells in 48 hours as determined by radioimmunoassay, said cells comprising

non-human DNA sequences that control transcription of DNA encoding human erythropoietin.

3. Vertebrate cells according to claim 1 capable of producing in excess of 1000 U erythropoietin per 106cells in 48 hours.

4. Vertebrate cells which can be propagated in vitro which comprise transcription control DNA sequences, other than human erythropoietin transcription control sequences, for production of human erythropoietin, and which upon growth in culture are capable of producing in the medium of their growth in excess of 100 U of erythropoietin per 106 cells in 48 hours as determined by radioimmunoassay.

6. Vertebrate cells according to claim 4 capable of producing in excess of 1000 U erythropoietin per 106cells in 48 hours.

7. A process for producing erythropoietin comprising the step of culturing, under suitable nutrient conditions, vertebrate cells according to claim 1, 2, 3, 4, 5, or 6.

Each of the claims contain the limitation "non-human DNA sequences that control transcription" that appears in claim 1 of the '349 patent or the limitation "transcriptional control DNA sequences, other than human erythropoietin transcription control sequences" that appears in claim 4 of the '349 patent. Transcription is the process whereby RNA polymerase copies genetic information contained in a DNA nucleotide sequence into an RNA sequence. It is a critical step in the expression of proteins like erythropoietin and is itself controlled by specific DNA sequences. According to the patent, "transcription control sequences" is the collective term for DNA sequences that not only "provide a site for initiation of transcription into mRNA," but also are capable of binding proteins that determine "the frequency (or rate) of transcriptional initiation." '349 patent, col. 2, lines 3-12.

Amgen contended that this phrase means "non-human DNA sequences that are able to initiate or regulate RNA synthesis from EPO DNA." TKT argued that the phrase means "DNA sequences which did not originate in the human genome, which initiate and regulate RNA synthesis of adjacent DNA, and which replace the human EPO transcription control sequences." By including the term "adjacent DNA" in its construction, TKT sought to require the DNA sequences that control transcription to be located in a position adjacent to the gene segment intended to be expressed. Furthermore, TKT contended that in order to "control" transcription, the DNA sequences must both initiate and regulate the transcription of a gene. Amgen objected to the use of "and," preferring a construction that required DNA sequences either to initiate or regulate transcription. Finally, the parties disagreed as to the meaning of "non- ***1413** human." Amgen argued that "non-human" means "not part of the human genome," whereas TKT contended it meant "not originating in the human genome." [FN17]

First, the court rejected TKT's position and concluded that "non-human" DNA sequences are DNA sequences that are "not part of the human genome." The court similarly rejected TKT's "adjacent" language because "no claim term could reasonably be construed to be limiting the transcription control DNA sequences by their location." Finally, the court held that DNA sequences that control transcription are DNA sequences that initiate and regulate the processes of transcription. *Amgen*, 126 F.Supp.2d at 88, 57 USPQ2d at 1459-60.

The district court entered judgment of noninfringement for TKT on method claim 7 of the '349 patent under an identical rationale to that used to grant judgment of noninfringement for the method claims of the '698 patent. *Id.* at 122, 57 USPQ2d at 1486. As we have found the court's analysis with respect to the '698 patent to be legally unsupportable, *see supra* at 41- 42, we likewise vacate the district court's judgment with respect to claim 7 of the '349 patent and remand for further consideration. As to the product claims of the '349 patent, the court held that each of claims 1, 3, 4, and 6 were literally infringed, and further held (alternatively) that claims 3 and 6 were equivalently infringed. [FN18]

Aside from the challenge, already rejected, to the trial court's construction of the term "vertebrate cells," TKT mounts a weak challenge to these findings of infringement apparently under the

reverse doctrine of equivalents. [FN19]

Under the reverse doctrine of equivalents, an accused product or process that falls within the literal words of a claim nevertheless may not infringe if the product or process "is so far changed in principle from a patented article that it performs the same or a similar function in a substantially different way." *Graver Tank & Mfg. Co. v. Linde Air Prod. Co.*, 339 U.S. 605, 608-09, 85 USPQ 328, 330 (1950); *see generally* Donald S. Chisum, 5A *Chisum on Patents*§ 18.04 (1999). This doctrine is equitably applied based upon underlying questions of fact, *see Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1581, 18 USPQ2d 1001, 1013 (Fed. Cir. 1991), when the accused infringer proves that, despite the asserted claims literally reading on the accused device, "it has been so changed that it is no longer the same invention." *Del Mar Avionics, Inc. v. Quinton Instr. Co.*, 836 F.2d 1320, 1325, 5 USPQ2d 1255, 1259 (Fed. Cir. 1987) (citing *Graver Tank*, 339 U.S. at 608-09).

[12] We are not persuaded by TKT that this is a case where equity commands a determination of non-infringement despite its product literally falling within the scope of the asserted claims. TKT relies on findings of the district court regarding differences in the way the accused device controls transcription in the '698 patent. It is true, as Amgen candidly admits, that the method by which TKT controls transcription is not identical. Whereas the patent describes placing the promoter DNA in close proximity, or even adjacent, to the EPO leader peptide, TKT places its promoter further upstream. But again, it is error to conduct infringement analyses in a vacuum, without reference to the claims at issue.

The vertebrate cells of the '349 patent, as claimed, are comprised of non- human DNA sequences that control transcription of DNA encoding human erythropoietin. And ***1414** "control[ling] transcription of DNA encoding human erythropoietin" simply means initiating and regulating the process of transcription. *Amgen*, 126 F.Supp.2d at 88, 57 USPQ2d at 1460. This limitation is met literally because the cytomegalovirus in TKT's R223 cells performs this function, *id.* at 118, 57 USPQ2d at 1484, notwithstanding TKT's reliance on the court's erroneous analysis of the '698 patent method claims.

IV

Our affirmance of the district court's findings that certain of the asserted claims are infringed is not yet the coup de grace for TKT; non-frivolous validity issues remain. One of the statutory requirements for patentability is that the invention for which a patent is sought was not known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention by the applicant. *See* 35 U.S.C. § 102(a). Similarly, one is not entitled to a patent if the subject matter of the invention as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the invention is directed. *See id.* § 103. TKT relies particularly on two items of prior art that allegedly render certain of the asserted claims anticipated under § 102(a) or obvious under § 103. We discuss each in turn.

A

TKT contends the asserted claims are anticipated by the work of Dr. Eugene Goldwasser ("Goldwasser"). Beginning in 1979-80, Goldwasser conducted a clinical study at the University of Chicago at Illinois in which he obtained a preparation of highly purified erythropoietin derived from human urine and administered approximately 10,000 units of human urinary EPO to three anemic patients. *Amgen*, 126 F.Supp.2d at 111, 57 USPQ2d at 1478. Although this study showed an increase in reticulocyte count in all three patients, and an increase in erythroid cells, plasma iron clearance rate, and red cell mass in at least one patient, Goldwasser admitted that "[t]here was no significant change in hematocrit in any patient." *Id.* at 111-12, 57 USPQ2d at 1478. And because there was no increase in hematocrit, Goldwasser testified in his deposition that he considered the study a failure. The district court concluded, as a result, that the study could not be invalidating anticipatory prior art: "[A]nother's experiment, imperfect and never perfected will not serve either as an anticipation or as part of the prior art, for it has not served to enrich it." *Id.* at 112, 57 USPQ2d at 1479 (quoting *Fromson v. Advance Offset Plate, Inc.*,

755 F.2d 1549, 1558, 225 USPQ 26, 33 (Fed. Cir. 1985)).

The district court similarly concluded that Goldwasser did not render the patents obvious. Of paramount importance to the court was the fact that the prior art references, including Goldwasser, lacked Amgen's disclosure of the genetic sequence of EPO and failed to describe any transcription control sequences. *Id.* at 115, 57 USPQ2d at 1481. The court also considered the secondary factors -- particularly long-felt need and commercial success -- to be of high importance. *Id.* at 116, 57 USPQ2d at 1482 ("Before the advent of Amgen's product, whether EPO could actually produce a sustainable increase in a patient's hematocrit was not known. Furthermore, Amgen's EPO product, which was the first EPO-containing pharmaceutical composition to obtain FDA approval, has greatly improved the quality of life of chronic renal failure patients throughout the world. As a result, Dr. Lin received widespread public acclaim for his work.").

TKT assigns error to the district court's alleged blind acceptance of Goldwasser's assertion that the test was a failure without considering the contemporaneous testimony of Goldwasser's collaborator, Dr. Baron, who reported to the Food and Drug Administration in 1984 that evidence of erythroid marrow stimulation was detected. In particular, according to TKT, the court erred by failing to "look[] at the definition of therapeutic effect in the specification." We agree that "therapeutically effective" must be defined in accordance with *Markman v. Westview Instruments* before this issue can be properly resolved, and we therefore vacate and remand for further proceedings with respect to Goldwasser.

For the *Markman* hearing in this case, ten terms were "pre-selected" based upon their relationship to Amgen's then-pending motion for summary judgment of infringement. *Id.* at 81, 57 USPQ2d at 1455. Whether those "pre-selected" terms were chosen by the court or the parties is unclear from the record, but ***1415** what is clear is that "therapeutically effective" was not among them. And so the district court, assumedly viewing "therapeutically effective" as not in dispute, construed it in its discussion of the Goldwasser reference:

> Such evidence [of, e.g., increased erythroid marrow stimulation] should be outweighed by the fact that the *actual* production of mature red blood cells was not achieved and, as a result, hematocrit levels were unchanged. *Because an increase in hematocrit and hemoglobin levels is the true mark of therapeutic effectiveness*, Dr. Goldwasser's study, which revealed only inchoate indicators of red blood cell production, falls far short of anticipating claims requiring a therapeutic amount of human EPO. *Id.* at 112, 57 USPQ2d at 1479 (second emphasis ours). Had "therapeutically effective" not been in dispute, no error would arise. A district court may -- indeed, often must -- interpret or define a term in the claims that is not in dispute in order to provide a proper context for the discussion of the terms that are in dispute. *See, e.g., DeMarini Sports v. Worth, Inc.*, 239 F.3d 1314, 1323, 57 USPQ2d 1889, 1893-94 (Fed. Cir. 2001). But here, the term "therapeutically effective" is in dispute because it is central to whether Goldwasser is properly considered prior art. *See In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985) (holding that a non-enabled disclosure will not suffice as § 102 prior art).

Although the endgame in the treatment of chronically anemic patients is to increase the hematocrit, as recognized by the district court, the claim term "therapeutically effective" must be understood in light of the specification of which it is a part. And that specification appears to teach that results in addition to simply an increase in hematocrit can provide effective therapy. *See* '933 patent, col. 33, lines 19-31 ("[The claimed polypeptide products] are conspicuously suitable for use in erythropoietin therapy procedures . . . to develop any or all of the effects heretofore attributed in vivo to EPO, *e.g., stimulation of reticulocyte response . . ., erythrocyte mass changes . . ., and, as indicated in Example 10, increasing hematocrit levels in mammals*." (emphasis added)).

> [13] Amgen asserts that the district court's construction of "therapeutically effective" is supported by admissions of TKT's experts that the term means "increasing and maintaining the patient's hematocrit to normal or near normal levels." But the relevant question is not whether one of ordinary skill would so understand the term, but whether that term should be limited based upon the express disclosure in the

specification. *CCS Fitness*, 288 F.3d at 1367, 62 USPQ2d at 1662-63 ("[A] claim term will not carry its ordinary meaning if the intrinsic evidence shows that the patentee distinguished that term from prior art on the basis of a particular embodiment, expressly disclaimed subject matter, or described a particular embodiment as important to the invention."). If the claim term "therapeutically effective" encompasses the patient responses described in the specification, as it appears to us it does, then the Goldwasser study may constitute invalidating prior art under § 102(a) or § 103 even if he did not achieve his intended result. We therefore vacate the trial court's determination that Goldwasser cannot constitute prior art because the study was a failure. Resolution of the issue turns on the construction of the meaning of "therapeutically effective," which the trial court should have an opportunity to construe in the first instance under *Markman* principles. *See Bayer AG v. Biovail Corp.*, 279 F.3d 1340, 1349, 61 USPQ2d 1675, 1682 (Fed. Cir. 2002). Accordingly, on remand, the court should construe this term and, in light of that construction, should determine whether Goldwasser invalidates any of the asserted patents under 35 U.S.C. §§ 102(a) or 103. [FN20]

B

A second item of prior art germane to this appeal is United States Patent No. 4,377,513 ("Sugimoto"), issued in March 1983. Sugimoto discloses a process for producing human erythropoietin "characterized by multiplying human lymphoblastoid cells capable of producing human erythropoietin by transplanting said cells into a non-human warm-blooded animal body, or alternatively multiplying said ***1416** cells by allowing said cells to multiply with a device by which the nutrient body fluid of a non-human warm-blooded animal is supplied to said cells, and allowing the cells multiplied by either of the above multiplication procedures to release human erythropoietin."Sugimoto, col. 1, lines 30-38. Given the similarity of Sugimoto's disclosure to the patents asserted by Amgen, TKT naturally raised Sugimoto as potentially invalidating prior art, even though Sugimoto had been before the examiner.

The district court concluded that Sugimoto was not prior art under 35 U.S.C. § 102(a) because it was not proven to be enabled. *Amgen*, 126 F.Supp.2d at 108, 57 USPQ2d at 1476 ("In light of the intense competition that grew out of the race to make human EPO suitable for treatment of chronic anemia, one would imagine that if Sugimoto's invention were truly enabling, then he would have won that lucrative race."). On appeal, TKT argues that the trial court erred in placing on it the burden of proving enablement of Sugimoto, because United States patents -- even those only asserted as prior art in an invalidity defense -- are presumed enabled under 35 U.S.C. § 282. We agree that prior art patents are presumed enabled, but under authority going beyond § 282.

A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled. Long ago our predecessor court recognized that a non-enabled disclosure cannot be anticipatory (because it is not truly prior art) if that disclosure fails to "enable one of skill in the art to reduce the disclosed invention to practice." *In re Borst*, 345 F.2d 851, 855, 145 USPQ 554, 557 (C.C.P.A. 1962) ; *accord In re Donohue*, 766 F.2d at 533, 226 USPQ at 621. Thus, the critical issue here is not whether Sugimoto must be enabled, but rather whether it is the plaintiff or the defendant who bears the burden of proof with respect to that question.

On appeal, Amgen argues that there should be no presumption of enablement in this case because under § 282 courts only presume the claimed subject matter in a patent is enabled. Thus, Amgen argues, because only the unclaimed disclosures of Sugimoto are at issue here, no presumption of enablement should apply. This argument is not relevant, however, because, as reasoned below, we do not only rely on § 282 as the source for a presumption. Instead, relying on our precedent, we hold a presumption arises that both the claimed and unclaimed disclosures in a prior art patent are enabled.

[14] In patent prosecution the examiner is entitled to reject application claims as anticipated by a prior art patent without conducting an inquiry into whether or not that patent is enabled or whether or not it is the claimed material (as opposed to the unclaimed disclosures) in that patent that are at issue. [FN21] *In re Sasse*, 629 F.2d 675, 681, 207

> USPQ 107, 111 (C.C.P.A. 1980) ("[W]hen the PTO cited a disclosure which expressly anticipated the present invention . . . the burden was shifted to the applicant. He had to rebut the presumption of the operability of [the prior art patent] by a preponderance of the evidence." (citation omitted)). The applicant, however, can then overcome that rejection by proving that the relevant disclosures of the prior art patent are not enabled. *Id.* We hold that an accused infringer should be similarly entitled to have the district court presume the enablement of unclaimed (and claimed) material in a prior art patent defendant asserts against a plaintiff. Thus, a court cannot ignore an asserted prior art patent in evaluating a defense of invalidity for anticipation, just because the accused infringer has not proven it enabled. Like the applicant in *ex parte* prosecution, however, the patentee may argue that the relevant claimed or unclaimed disclosures of a prior art patent are not enabled and therefore are not pertinent prior art. If a patentee presents evidence of nonenablement that a trial court finds persuasive, the trial court must then exclude that particular prior art patent in any anticipation inquiry, for then the presumption has been overcome. [FN22] Therefore, it was Amgen who bore ***1417** the burden of proving the nonenablement of Sugimoto before the district court. TKT did not bear a bear burden of proving enablement.

Turning now to the district court's opinion, we think a fair reading is that the court, at least implicitly, put a burden of proving enablement of Sugimoto on TKT. The court began its analysis of Sugimoto by discussing evidence from Amgen and concluding "one would imagine that if Sugimoto's invention were truly enabling, then he would have won that lucrative race [to make human EPO suitable for treating anemia]." *Amgen*, 126 F.Supp.2d at 108, 57 USPQ2d at 1476. Proceeding from that standpoint, the court analyzed whether TKT's evidence was sufficient "to counter" this apparent conclusion that Sugimoto was not enabled. *Id.* at 108-09, 57 USPQ2d at 1476. Next, the court concluded its discussion of the enablement of Sugimoto by stating "TKT provided no evidence adequate to overcome the presumption that the Patent Office correctly rejected the contention that Sugimoto was an anticipating reference." *Id.* at 109, 57 USPQ2d at 1477. Importantly, only after apparently concluding that Sugimoto was not enabled did the district court discuss whether Sugimoto contained each and every limitation of any of Amgen's claims. The logical implication being that the court concluded that because TKT had not proven the enablement of Sugimoto, it could not anticipate any of Amgen's claims. In sum, we determine that ultimately, the district court placed the burden of proving the enablement of Sugimoto on TKT.

In addition, looking at the evidence Amgen did present, we cannot conclude the district court properly found Amgen had met any burden that the court did place on it. At trial Amgen's expert, Dr. Erslev, testified that "no one reported using Sugimoto's process to make a pharmaceutical composition of human EPO, nor has any patient ever been treated by any EPO produced by the Sugimoto procedure." *Id.* at 108, 57 USPQ2d at 1476. The mere fact that no one *has* so used the Sugimoto process is only minimally probative of non-enablement: a conclusion that no one *could have* used Sugimoto. Amgen also pointed out that Sugimoto was before the patent examiner during the prosecution of Amgen's patents. *Id.* While this was true, Sugimoto's non-enablement was only one of several arguments Amgen presented to overcome a rejection during prosecution and the examiner did not state his agreement with this position when he allowed the patent. Because we cannot assume the acceptance of every argument presented during prosecution, the mere fact this argument was made is also only minimally probative of the enablement of Sugimoto. In sum, the evidence presented by Amgen was insufficient to meet the burden Amgen apparently was assigned.

We must therefore conclude that to the extent it placed a burden on TKT the district court committed error. However, we hold this error to be, for the most part, harmless. After analyzing enablement and apparently finding the relevant unclaimed disclosures of Sugimoto nonenabled, the court nevertheless conducted a full anticipation analysis. Indeed, the district court performed a detailed analysis of each piece of anticipating prior art -- including Sugimoto -- asserted against each of Amgen's claims. *Id.* at 109-10, 57 USPQ2d at 1477. From this analysis the court found that "none of the cited references disclose [sic] each and every limitation of any of Amgen's individual claims." *Id.*

at 109, 57 USPQ2d at 1477. It does not appear that TKT has argued this alternative finding was clear error. However, we do not rest on waiver, but affirm the district court's finding that Sugimoto does not anticipate any asserted claims of the '080, '349, or '698 patents because from our review of the evidence and the subsidiary finding of the court, it was not clear error to find in each claim one or more limitations not disclosed in Sugimoto. But given our earlier holdings, we must vacate and remand the finding that Sugimoto does not anticipate claim 1 of the '422 patent. On remand, the district court should consider whether claim 1 of the '422 patent is novel over Sugimoto in light of the court's new definition of "therapeutically effective" and while mindful of the principle that source limitations cannot impart novelty to old compositions.

> [15] Our review is not yet finished, however, because it is apparent from the district court's opinion that TKT relied upon Sugimoto to assert invalidity of the patents in suit under both § 102 and § 103. In its obviousness ***1418** inquiry, the district court disregarded Sugimoto because it concluded it was not enabled. It recognized, however, the important and potentially dispositive role that Sugimoto would have otherwise played in the obviousness analysis:

Had the court concluded otherwise [ *i.e.*, that Sugimoto was enabled], the Sugimoto patent would go a long way toward proving TKT's obviousness defense. As explained above, Sugimoto disclosed EPO-producing fused cells and advised that (1) conventional techniques can be utilized to achieve purification and (2) the human EPO produced thereby can be used in pharmaceutical compositions for the treatment of anemia. Thus, the patent itself suggested combining its invention with prior art sources relating to both purification and therapeutic delivery. Provided that one of ordinary skill in the art could actually make the EPO-producing cells described in the Sugimoto patent, a point on which TKT failed to persuade this court, such a combination of prior art materials might render invalid the pharmaceutical composition claims of the '933, '080, and '422 patents. *Id.* at 114 n.29, 57 USPQ2d at 1480 n.29. Under § 103, however, a reference need not be enabled; it qualifies as a prior art, regardless, for whatever is disclosed therein. *See Symbol Tech., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1578, 19 USPQ2d 1241, 1247 (Fed. Cir. 1991); *Reading & Bates Constr. Co. v. Baker Energy*, 748 F.2d 645, 652, 223 USPQ 1168, 1173 (Fed. Cir. 1984). Therefore, the district court's obviousness holdings with respect to Sugimoto are vacated and remanded. On remand, the district court should reconsider obviousness with respect to Sugimoto, but should do so without reference to whether Sugimoto is enabled, as enablement of the prior art is not a requirement to prove invalidity under § 103.

V

The last issue on appeal is inequitable conduct. TKT raised before the district court essentially three instances of allegedly inequitable activities by the patentee: withholding crucial details regarding the Goldwasser study; withholding certain results of its own experiments that undermined the validity of the '933 patent; and failing to disclose to the Patent and Trademark Office the existence of this litigation. The district court found that TKT had not proven inequitable conduct by clear and convincing evidence, and we have not been persuaded on appeal that a contrary result is compelled. In reaching this conclusion, we need look no further than the district court's determination that TKT's case was doomed because it was bereft of evidence of intentional deception:

> TKT has failed to produce any persuasive evidence that causes the Court to doubt the integrity of the individuals who bore the duty of shepherding the Amgen patent applications through the Patent and Trademark Office, [so] its charge of inequitable conduct utterly fails . . . . TKT has failed to prove by clear and convincing evidence that this [experimental] data was material or that it was withheld with intent to deceive . . . . [And] TKT has not even begun to demonstrate that Amgen representatives possessed an intent to deceive the [PTO] in failing to provide specific notification regarding this litigation . . . . In summary, TKT's proof of inequitable conduct with respect to each of these charges falls short of the mark. Although the directness of Amgen's disclosures varies depending on the particular piece of disputed information, one truth remains the same throughout: Amgen's representatives never intended to deceive the Patent Office. Consequently, a finding of inequitable

conduct would be error and the Court does not so find on the complete record. *Id.* at 141, 145, 147, 57 USPQ2d at 1500, 1504, 1505.

A patent applicant commits inequitable conduct when, during prosecution of the application, he makes an affirmative representation of a material fact, fails to disclose material information, or submits false material information, and does so with the intent to deceive. *Refac Int'l, Ltd. v. Lotus Dev. Corp.*, 81 F.3d 1576, 1581, 38 USPQ2d 1665, 1669 (Fed. Cir. 1996). As a general principle, materiality and intent are balanced -- a lesser quantum of evidence of intent is necessary when the omission or misrepresentation is highly material, and vice versa. *See, e.g., GFI, Inc. v. Franklin Corp.*, 265 F.3d 1268, 1273, 60 USPQ2d 1141, 1143 (Fed. Cir. 2001). At the same time, however, there must be some ***1419** threshold showing of intent to be balanced; we will not find inequitable conduct on an evidentiary record that is completely devoid of evidence of the patentee's intent to deceive the PTO. *See Allen Eng'g Corp. v. Bartell Indus., Inc.*, No. 01-1238, 2002 U.S. App. LEXIS 15418, at *33 (Fed. Cir. Aug. 1, 2002) ("Materiality does not presume intent, which is a separate and essential component of inequitable conduct." (quoting *Allen Organ Co. v. Kimball Int'l, Inc.*, 839 F.2d 1556, 1567, 5 USPQ2d 1769, 1778 (Fed. Cir. 1988))).

Here, the district court determined that there was no evidence of intent to deceive, and TKT has directed us to none on appeal. Thus, to conclude the Amgen patents are unenforceable -- as TKT requests -- we must conclude (1) that the district court clearly erred by failing to find the minimal requisite intent to deceive, and (2) that it abused its discretion in weighing the degree of materiality against the degree of deceptive intent and by not then rendering the patents unenforceable. On the record before us, we decline to do so.

## CONCLUSION

We summarize our decision as follows. Affirmed are: the district court's claim construction; its finding that all of the patents in suit are enforceable; its finding that the '933 patent is invalid; and its finding that the '349 (product claims only) and the '422 patents are infringed. We vacate: its finding that the '933 patent was not infringed; several of its validity findings with respect to the '080, the '349, the '422, and the '698 patents; and its infringement findings with respect to the '698 patent and '349 patent claim 7. On remand, the district court should: construe the claim term "therapeutically effective" and then reconsider validity under §§ 102 and 103 in view of Goldwasser; reconsider validity of all asserted claims under § 103 and claim 1 of the '422 patent under § 102 in view of Sugimoto, with Amgen bearing the burden of proof on its non-enablement (for § 102 purposes only); reassess infringement of the accused method by comparing it solely to the limitations of each of the asserted method claims; and reevaluate its finding of infringement under the doctrine of equivalents of the '080 patent, focusing on the application of prosecution history estoppel.

AFFIRMED IN PART, VACATED IN PART, REMANDED.

No costs.

FN1. For further reading on these subjects, *see generally* Robert A. Meyers, ed., *Molecular Biology and Biotechnology: A Comprehensive Desk Reference*, VCH Publishers (1995); Benjamin Lewin, *Genes VII*, Oxford Univ. Press (2000); James D. Watson et al., *Recombinant DNA* (2d ed. 1992).

FN2. An "expression vector" is a circular piece of DNA (or "plasmid") that is inserted into a host cell to produce (or "express") a protein. The expression vector carries the gene encoding for the protein of interest (in this case human EPO), a marker that assures that the vector is properly introduced into the host cell, and a promoter site that the host will recognize to transcribe the vector's DNA. *See generally* Thomas E. Crieghton, ed., *Encyclopedia of Molecular Biology*, vol. 2, John Wiley & Sons, Inc. (1999) at 883-86.

FN3. Because the patents in suit share an identical disclosure, all citations will be to

the '933 specification unless otherwise noted.

FN4. That is not to say that there are no claims that have such a limitation. Unasserted claim 3 of the '933 patent, for example, does contain such a limitation: "A non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin . . . ." col. 38, lines 26-29.

FN5. We do not hold that these limitations lack meaning, only that they mean just what they say. Accordingly, they limit only the source from which the EPO is obtained, not the method by which it is produced.

FN6. We addressed this point in our claim construction analysis on pages 17-18 *ante*, finding that the written description did not exclude human cells from the scope of the claims. That analysis suffices here as well.

FN7. Indeed, Amgen's patents appear to satisfy the sequence requirement in *Eli Lilly* insofar as Figure 6 of the patents expressly discloses the complete (albeit slightly incorrect) sequence of human genomic EPO DNA and the encoded DNA.

FN8. There is no issue here as to *in haec verba* description because, as stated in the body of the opinion, in contrast to "cDNA" -- that clearly does not describe the actual sequence of the cDNA -- the words "mammalian cells" and "vertebrate cells" convey exactly what they are. Thus, this aspect of the holding in *Eli Lilly* is also inapplicable here.

FN9. TKT refers here to the district court's statement that "it appears that Dr. Lin claimed far more than he delivered." *Amgen*, 126 F.Supp.2d at 158, 57 USPQ2d at 1514. Although this statement does seem out of kilter with the court's ultimate holding, we understand it in light of how close the court viewed the issue: "After much reflection, the court finds that Amgen survives [the enablement challenge], albeit barely." *Id.* at 157, 57 USPQ2d at 1513.

FN10. Following the dissent's "machine" analogy, the "machine" is a genetically altered vertebrate cell containing transcription control sequences used to transcribe a human EPO gene to express the claimed levels of human EPO. Simply altering the way the human EPO gene is inserted or activated -- whether it be through transformation with exogenous DNA or through activation of an endogenous gene -- does not make this a different "machine"once built; rather, it only changes the way it was "constructed."

FN11. In this same vein, the dissent suggests that our court here has somehow "waived" the requirements of § 112 for product claims.

FN12. The court declined to rule on this issue at the *Markman* hearing, instead choosing to take the matter under advisement. *See* 126 F.Supp.2d at 87, 57 USPQ2d at 1459.

FN13. The district court held that every other limitation of the asserted claims in the '698 patent were met literally by the accused product/process. *Amgen*, 126 F.Supp.2d at 132-33, 57 USPQ2d at 1493. Thus, whether equivalent infringement occurred turned on whether the "Figure 6" limitation was equivalently met.

FN14. Amgen argues: "The specification describes the mature amino acid sequence

of human EPO as 'including' -- not 'limited to' -- the 1-166 sequence. Properly construed, Lin's claimed sequence -- the mature sequence -- includes the fully processed form of any glycoprotein having the Figure 6 sequence. That includes both the 1-165 and the 1-166 amino acid sequences of Figure 6. Only this construction affords 'mature'its proper meaning, and includes Lin's preferred embodiment."

FN15. Claim 5 claims "[t]he process of claim 4 wherein said promoter DNA is viral promoter DNA." Claim 7 claims "[th]e process of claim 6 wherein said vertebrate cells further comprise amplified marker gene DNA." Claim 8 claims "[t]he process of claim 7 wherein said amplified marker gene DNA is Dihydrofolate reductase (DHFR) gene DNA." And claim 9 claims "[t]he process according to claims 2, 4 and 6 wherein said cells are mammalian cells."

FN16. The basis for this argument is that claim 2 of the '698 patent recites recombinant EPO "isolated from the host cell or the medium of its growth." Therefore, asserts TKT, "Amgen also knew how to claim what it now seeks, but failed to do so."

FN17. The importance of this distinction is that, because it is scientifically arguable that viral DNA originates in the human genome, the viral promoter DNA that TKT employs thus might not fall within the meaning of the claim.

FN18. We note also that the trial court granted summary judgment of infringement of the product claims of the '349 patent. It modified its summary judgment finding (but reached the same result) with respect to the "controlling transcription" limitation in light of extensive trial testimony. *Amgen*, 126 F.Supp.2d at 118, 57 USPQ2d at 1485. Accordingly, unlike the other limitations in the '349 patent, we review the court's conclusion with respect to "controlling transcription" for clear error, even though it comes to us from a grant of summary judgment of infringement. Because TKT has not demonstrated clear error in the trial court's conclusion, we affirm the finding of infringement.

FN19. The sum total of TKT's challenge to the infringement finding, aside from the "vertebrate" issue, is as follows: "[TKT] also do[es] not use the 'transcription control sequences' of the '349 patent. As the court found, [TKT]'s transcription control sequences are not only structurally different from Amgen's sequences but also function in a different way. Because of those differences in structure and function, [TKT] do[es] not infringe the 'transcription control sequences' limitation in the '349 claims."

FN20. We note also that on remand when considering obviousness and anticipation issues relating to the '080 and '422 patents the district court should be cognizant of the rule that a claimed product shown to be present in the prior art cannot be rendered patentable solely by the addition of source or process limitations. *General Electric Co. v. Wabash Co.*, 304 U.S. 364, 373 (1938); *Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293, 311 (1884).

FN21. Additionally, we think it unwise as a matter of policy to force district courts to conduct a mini-trial on the proper claim construction of a prior art patent every time an allegedly anticipating patent is challenged for lack of enablement. As we frequently revisit district courts' determinations in matters of claim construction and validity, we are certainly aware that such a task can occupy a great deal of a court's resources. In any event, because the presumption outlined here

does not rely on § 282, we see no reason to impose these burdens on litigants and the district courts.

FN22. We note that by logical extension, our reasoning here might also apply to prior art printed publications as well, but as Sugimoto is a patent we need not and do not so decide today.

Clevenger, J., dissenting in part.

I join my colleagues' thorough opinion in all respects save one, albeit significant, exception. Because the claims lack meaningful limitations on the structure of the erythropoietin-producing cells, I cannot agree that the district court should have abstained from inquiring fully whether the claims were suspect under the enablement and written description provisions of 35 U.S.C. § 112, ¶ 1.

As described by the specifications of the patents in suit, Amgen in 1984 cloned and sequenced the DNA encoding human erythropoietin (EPO). Amgen then showed that by introducing the cloned EPO DNA (linked to a promoter sequence) into mammalian cells, those cells could be engineered to express high levels of functional human EPO protein. The parties refer to this as "exogenous DNA" expression of EPO. Amgen obtained several patents that cover the use and manipulation of cloned EPO DNA, and these patents, battle-tested through litigation, have been the foundation of Amgen's successful business of manufacturing and selling recombinant EPO. But these patents are not in suit here, and TKT's method for producing EPO does not rely upon manipulation of cloned EPO DNA or "exogenous DNA" expression technology.

The claims in suit here contain no significant limitations as to how the recombinant EPO is expressed, or as to the structure of the EPO-producing cells, so long as the EPO is "non-naturally occurring" or produced in "vertebrate cells." The central question in this case is therefore whether Amgen's disclosure of *one* means of producing synthetic EPO in mammalian cells, namely exogenous DNA expression, entitles it to claim *all* EPO produced by mammalian cells in culture, or *all* cultured vertebrate cells that produce EPO. I think this is a question of some importance. Yet it is a question that the district court simply refused to consider. Although the district court admitted that Amgen's disclosure was limited to exogenous DNA expression, the district court quite clearly and explicitly refused to decide whether the absence of any exogenous DNA limitations rendered the asserted claims vulnerable to the enablement challenge mounted ***1420** by TKT under section 112. According to the district court, because the asserted claims were to "compositions" rather than "processes," "the specification need teach only one mode of making and using a claimed composition." *Amgen Inc. v Hoescht Marion Roussel, Inc.*, 126 F.Supp.2d 69, 160, 57 USPQ2d 1449, 1515 (D. Mass. 2001). *See also id.* at 160, 164 n.57, 57 USPQ2d at 1516, 1518 n.57. Likewise, the district court refused to inquire whether the absence of limitations on the means of EPO expression raised questions of compliance with the written description requirement, holding that such an inquiry was irrelevant to composition claims. *Id.* at 150-51, 57 USPQ2d at 1508.

With respect to the '080 and '422 patents, which claim "non-naturally occurring" EPO and EPO "purified from mammalian cells grown in culture," the majority, like the district court, essentially passes over the question of whether these limitations--which are essential for patentability of the claims--raise issues of compliance with the enablement and written description requirements of section 112. The majority holds that patentees are free to decorate their composition claims with source and process limitations without any concern for whether the full scope of those limitations is enabled or described, and that these requirements of section 112 are waived so long as the patentee succeeds in characterizing its claims as "product" claims. Competent patent attorneys should be quick to take advantage of the majority's broad exemption from the disclosure requirements by the appropriate phraseology. Rather than endorse the district court's elevation of form over substance, I would vacate its decision on these issues regarding the '080 and '422 patents, and remand for further consideration in light of the vast scope of the claims in suit for which there appears to be insufficient enabling disclosure or written description.

With particular reference to the '349 patent, which

claims not EPO polypeptides but the cells that produce them, I think the district court's abstention from scrutiny under section 112 is even more patent error. The majority focuses on the district court's findings that the invention could readily be practiced in mammalian or vertebrate cells other than the hamster and monkey cells taught by the specification. I agree that TKT has not shown error in these findings. But, as it did for the EPO claims, the district court simply refused to consider whether the absence of any exogenous DNA limitations raised enablement issues, "[b]ecause Amgen is only required to enable skilled artisans to make its claimed product by only one method . . . ." *Id.* at 164 n.57, 57 USPQ2d at 1518 n.57. For the EPO-secreting cells, the absence of an exogenous DNA limitation is not a failure to limit how the product is made, but a failure to limit the structure of the claimed product itself. A cell, as employed in the patents in suit, is nothing more than a biological machine for making EPO. Even in more predictable arts, one who is first to make a machine is not entitled as a matter of law to claim any or all machines so long as they perform the same function. I would think it uncontroversial that even one who is first to make polymer X or alloy Y cannot obtain a claim as broad as "A machine that makes polymer X," or "A process that yields alloy Y," without reciting additional limitations that define the structure of the claimed machine or the steps necessary to carry out the claimed process.

Yet that is exactly what the district court and the majority allow the '349 patent to achieve. It claims any or all cultured vertebrate cells that can secrete a defined amount of EPO, with only a single limitation on their structure: that they "compris[e] non-human DNA sequences which control transcription of DNA encoding human erythropoietin," or that they "comprise transcription control DNA sequences, other than human erythropoietin transcription control sequences, for production of human erythropoietin." This is little more precise than a recitation of "A machine that makes polymer X, wherein the machine comprises means for controlling how much polymer X is made." The specification teaches only a single means by which the use of a transcription control sequence can coax a vertebrate cell to secrete EPO: by transforming that cell with an exogenous expression vector on which the transcription control sequence is linked to cloned EPO DNA. Yet the claims leave this essential aspect of the invention undefined. It is black-letter law that claims failing to recite a necessary element of the invention fail for lack of an enabling disclosure, *In re Mayhew*, 527 F.2d 1229, 1233, 188 USPQ 356, 358 (CCPA 1976) , and that ***1421** disclosure of one or two species may not enable a broad genus under these circumstances. *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1444-45 (Fed. Cir. 1991). At the very least, the absence of structural limitations in the '349 patent raises questions of its enablement, and I cannot agree that the district court chose correctly by ignoring those questions altogether. We should vacate the district court's judgment that the '349 patent passes enablement muster, and require the court to apply the correct law to the plain facts.

I must also disagree with the majority that the district court's approach was faithful to this court's articulation of the written description requirement of section 112, as expressed in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 45 USPQ2d 1498 (Fed. Cir. 1998). *Eli Lilly* articulated two principles of the written description requirement: that in *haec verba* description of broadly described generic subject matter may not suffice to describe the subject matter of that particular claim, 119 F.3d at 1567, 43 USPQ2d at 1404-05, and that disclosure of a species may not suffice to describe a genus, *id.* at 1568-69, 43 USPQ2d at 1405-06. The district court followed neither of these principles here, and the majority, dismissing *Eli Lilly* on the grounds that no undisclosed DNA molecule appears in this case, verges on confining *Eli Lilly* to its facts.

Nor am I convinced that the district court's approach was faithful to *Gentry Gallery*. In *Gentry*, only those claims that included limitations such as "wherein the control means are located on the console" satisfied the written description requirement. Because the specification failed to disclose any location for the controls other than on the console, those claims that lacked such limitations were invalid under § 112, ¶ 1. 134 F.3d at 1479-80, 45 USPQ2d at 1503-04. The question here is similar: whether the claims fail the written description requirement for lack of "exogenous DNA" limitations, because the specification discloses only the exogenous DNA technology that

was state of the art in 1984.

Even if we ignore the patents' statement that the claimed EPO molecules are "uniquely characterized by being the product of . . . expression . . . of exogenous DNA sequences" (which of course we cannot), I think the parallels between this case and *Gentry Gallery* are inescapable. The invalid claims in *Gentry* recited elements that could readily be found in the text of the specification (a couch, controls, a console), but those claims nonetheless failed the written description requirement because they included no limitations on how those elements were *arranged*. Likewise, the '349 claims--for which I think it must be conceded that structure of the EPO-secreting cell is a relevant question--recite particular elements found in the specification (cells, non-human control sequences, EPO-coding DNA), but do not include limitations on the arrangement of those elements, *e.g.* that the non-human control sequences and coding DNA are present on an exogenous expression vector in the cell. I agree that as a matter of claim interpretation there is no justification for importing an "exogenous DNA" limitation into the claims. But the absence of such limitations must weigh heavily in the section 112 inquiry, else we hold that claims become more resistant to written description challenges the more broadly drafted they are.

While I share my colleagues' admiration for the considerable efforts of the district court in this complicated case, I cannot share their faith that the district court properly and conscientiously applied *Eli Lilly* and *Gentry Gallery*, when the district court's opinion is completely devoid of reference either to those cases or to the principles they espouse. If the district court did not focus on the correct law to be applied, then its factual findings merit no deference, and the correct remedy for this omission is to vacate the district court's judgment on this point and remand for further consideration. Our precedent has little value if the district courts may overlook its certain pertinence, if not its plain applicability.

C.A.Fed.

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**(Cite as: 66 U.S.P.Q.2d 1429)**



**H**

Moba B.V.
v.
Diamond Automation Inc.

U.S. Court of Appeals Federal Circuit

Nos. 01-1063, -1083

Decided April 1, 2003

**PATENTS**
**[1] Patent construction -- Claims -- Broad or narrow (§ 125.1303)**
**Patent construction -- Claims -- Defining terms (§ 125.1305)**

**JUDICIAL PRACTICE AND PROCEDURE**
**Procedure -- Jury trials (§ 410.42)**
Federal district court improperly allowed jury to import additional limitation into court's claim construction in upholding jury's conclusion that "guiding steps" recited in claim of patent for egg sorting method must be performed sequentially, since court found that jury reasonably could have determined from testimony that sequential performance is necessary characteristic of "guiding steps" limitation, whereas claim construction is matter of law, and court's instructions to jury regarding "guiding steps" did not require sequential performance; patentee did not waive its right to argue interpretation of "guiding steps" on appeal, even though it did not object to district court's claim construction or its instructions to jury, since patentee does not seek to alter district court's construction on appeal, and has argued consistently that neither language of claim itself, nor court's order defining that language, requires that "guiding steps" occur separately.

**PATENTS**
**[2] Infringement -- Tests (§ 120.09)**
Infringement analysis for method claims that examines distinctions between implementing apparatuses is disfavored; in present case, accused infringer's argument for noninfringement of method claim for egg sorting is without merit, since it focuses on distinctions between device that implements accused method and patentee's preferred embodiment for claimed method, and since apparatus of accused method performs all three "guiding steps" recited in claim.
**[3] Infringement -- Literal infringement (§ 120.05)**
**Patent construction -- Claims -- Defining terms (§ 125.1305)**
**Patent construction -- Claims -- Process (§ 125.1309)**
Accused egg sorting device meets "holding station" limitation of asserted method claim, even though egg in accused method does not cease motion before being lifted to overhead conveyor, since claims do not require specific temporal limitation associated with term "holding," and ordinary meaning of "to hold" imposes no requirement that object remain stationary, since specification indicates that claimed process holds and moves egg at same time, and since term "holding station" thus does not require lack of motion.
**[4] Infringement -- Literal infringement (§ 120.05)**
**Infringement -- Doctrine of equivalents -- In general (§ 120.0701)**
**Patent construction -- Claims -- Process (§ 125.1309)**
Accused egg sorting method does not meet, either literally or under doctrine of equivalents, limitation of asserted method claim that requires rotation of egg receiving means "downwardly and away" from conveyor means, in order "to urge the received eggs downwardly," since, in context of patent, "to urge" should be given its broader meaning of "to cause to move," since accused infringer presented evidence that brush belt in device of accused method does not guide eggs downwardly relative to their initial position upon receipt in brush belt, and since device performs different function, in different way, to obtain different result from language of limitation.
**[5] Patentability/Validity -- Specification -- Written description (§ 115.1103)**
Compliance with written description requirement of 35 U.S.C. § 112 does not require particular form of disclosure, provided person of skill in art could determine from specification that inventor possessed invention at time of filing; in present case, patent for egg sorting method need not disclose conveyor lifting system encompassed by asserted claim, since specification describes every

element of claim in sufficient detail that one of ordinary skill in art would recognize that inventor possessed invention at time of filing.

**[6] Patentability/Validity -- Specification -- Enablement (§ 115.1105)**

Substantial evidence supports finding that claim for egg sorting method is not invalid for lack of enablement, since there is no evidence recounting amount of experimentation person of ordinary skill in art would require to develop conveyor lifting system in view of patent's disclosure, and since inference of undue experimentation cannot be drawn from limited general testimony concerning development of conveyor lifting system taken separate from disclosure of patent.

**PATENTS**

**Particular patents -- General and mechanical -- Egg sorting**

4,519,494, McEvoy and Thomas, egg handling system, judgment of noninfringement affirmed.

4,519,505, Thomas, egg transfer system, judgment of noninfringement reversed.

Appeal from the U.S. District Court for the Eastern District of Pennsylvania, Kauffman, J.

Action by Moba B.V., Staalkat B.V., and FPS Food Processing Systems Inc. against Diamond Automation Inc. for declaratory ***1431** judgment of patent invalidity and noninfringement, in which defendant counterclaimed for declaratory judgment of validity and infringement. Defendant appeals from jury verdict of noninfringement, and from denial of its motion for judgment of infringement as matter of law, and plaintiffs cross-appeal from judgment that asserted patent claims are not invalid. Affirmed in part, reversed in part, and remanded; Rader, J., concurring in separate opinion; Bryson, J., concurring in separate opinion.

Jon A. Baughman, Erik N. Videlock, and Nicole D. Galli, of Pepper Hamilton, Philadelphia, Pa.; Marvin Petry and Linda R. Poteate, of Larson & Taylor, Alexandria, Va., for plaintiffs/cross-appellants.

Albert J. Breneisen, John w. Bateman, and Sheila Mortazavi, of Kenyon & Kenyon, New York, N.Y., for defendant-appellant.

Before Rader, Schall, and Bryson, circuit judges.

Per curiam.

At trial, a jury in the United States District Court for the Eastern District of Pennsylvania found that Moba, B.V., Staalkat, B.V., and FPS Food Processing Systems, Inc.(collectively FPS) did not infringe patents assigned to Diamond Automation, Inc. (Diamond). *See Moba, B.V. v. Diamond Automation, Inc.*, No. 95-CV-2631, 2000 U.S. Dist. LEXIS 15483, at *43 (E.D. Pa. Sept. 29, 2000). In response to a motion for judgment as a matter of law (JMOL), the district court correctly discerned that substantial evidence supports the jury's verdict that machines sold by FPS and used by its customers do not practice the method of United States Patent No. 4,519,494 ('494 patent). However, no reasonable jury could find that machines sold by FPS and used by its customers do not practice the method of United States Patent No. 4,519,505 ('505 patent). Thus, this court affirms-in-part, reverses-in-part, and remands for a determination of damages.

I.

Diamond is a Michigan corporation that manufactures and sells high-speed egg processing machines to sort batches of eggs into different categories by weight and quality. Diamond developed these machines during the early 1980s with technology that significantly increased the processing speed for eggs. Diamond obtained various patents covering aspects of that technology, including the '494 and '505 patents, and United States Patent Nos. 4,569,444 ('444 patent) and 4,505,373 ('373 patent). While Diamond asserted all of these patents at trial, only the '505 and '494 patents appear in this appeal. The '505 patent relates generally to "front end" processing of eggs, while the '494 patent relates generally to "back end" processing of eggs.

The "front end" process first washes the eggs, then introduces them into a candling station where a high intensity light source checks the eggs for defects such as blood spots or cracks. The process then weighs the eggs. A computer stores this information for use in sorting the eggs at a later point. Figure 2 of the '505 patent illustrates an embodiment of the invention designed to weigh eggs and to lift them to an overhead conveyor.

Claim 24 of the '505 patent corresponds generally to the subject matter of Fig. 2:

24. A method for advancing a plurality of rows of eggs from a candling station through a plurality of weighing stations in an egg grading apparatus, comprising,

conveying eggs from said candling station to elongated guide means disposed adjacent to said candling station, continuously advancing said eggs on said guide means through said weighing stations,

simultaneously with said step of advancing, weighing said eggs at said weighing stations,

***1432** *guiding said eggs from said weighing stations first to a plurality of egg holding stations located downstream of said guide means and then to a plurality of locations longitudinally spaced-apart from and substantially horizontally co-planar with said holding stations*,

*guiding further eggs to said plurality of holding stations*, and lifting said eggs simultaneously from said holding stations and said plurality of longitudinally spaced-apart locations.

'505 patent, col. 13, ll. 33-54 (emphasis added).

The "back end" process receives eggs from "front end" processing and transfers them to an overhead conveyor. This conveyor carries the eggs in rows until dropping off each individual egg at a different receiving station based on the information in the computer. At each station, the eggs are either packaged or discarded. Figure 8 of the '494 patent illustrates an embodiment of the invention designed to receive eggs from an overhead conveyor for transport to a packer:

Claim 28 of the '494 patent corresponds generally to the subject matter of Fig. 8:

28. A method of transferring eggs delivered in spaced-apart aligned relationship by a first conveyor means to a receiving station, comprising the steps of,

delivering eggs to said receiving station in parallel spaced apart rows on said first conveyor means,

releasing eggs from said first conveyor means at the receiving station in accordance with a predetermined requirement,

positioning a receiving means below the first conveyor means so as to receive therein and deliver to a common member the eggs released from the parallel spaced-apart rows of the first conveyor means,

receiving said eggs in the receiving means disposed at said receiving station whereby the released eggs from both said parallel spaced apart rows of eggs fall on and are received by said receiving means,

*rotating the receiving means downwardly and away from said first conveyor means to urge the received eggs downwardly,*

guiding said eggs received in said receiving means downwardly and away from said receiving means, and

conveying said eggs away from said receiving means on second conveyor means,

said step of releasing comprising releasing said eggs successively from said first conveyor means at said receiving station along the length of said receiving means, and said step of conveying comprising conveying said eggs individually in rows away from said receiving means on said second conveyor means.

'494 patent, col. 12, ll. 9-40 (emphasis added).

Moba, B.V., and Staalkat, B.V., are Dutch companies that also manufacture and sell high-speed egg processing machines, such as the Moba Omnia and the Staalkat Selecta. FPS Food Processing, a Pennsylvania corporation, sells

Moba's and Staalkat's egg processing machines in the United States. In the United States market, FPS and Diamond are the only significant competitors in the manufacture and sale of high-speed egg processing machines.

In 1994, Diamond filed a patent infringement suit in the United States District Court for the Eastern District of Michigan against FPS. The district court dismissed that case for lack of personal jurisdiction. In 1995, FPS filed suit in the United States District Court for the Eastern District of Pennsylvania seeking a declaratory judgment that the '444, '494, ***1433** '373, and '505 patents are invalid and not infringed by the Moba Omnia and the Staalkat Selecta. Diamond filed a declaratory judgment counterclaim that the patents are valid and infringed. After discovery, the district court construed the patent claims. Then a jury heard the case from January 28, 2000 to February 25, 2000. On February 22, 2000, before the jury retired to consider its verdict, Diamond moved for entry of JMOL under Rule 50(a) of the Federal Rules of Civil Procedure that FPS infringed and induced infringement of the four patents. In its February 25, 2000 verdict, the jury found that those patents were not invalid and not infringed. On March 6, 2000, the district court denied Diamond's February 22, 2000 JMOL motion, and entered judgment in favor of Diamond on the validity issues and in favor of FPS on the infringement issues. Diamond renewed its motion for JMOL regarding infringement, which the district court again denied.

Diamond argues that claim 24 of the '505 patent and claim 28 of the '494 patent cover methods used in both the Moba Omnia and the Staalkat Selecta. Diamond also contends that FPS has induced its customers to infringe those claims by selling them the Moba Omnia and the Staalkat Selecta and by training them to use those machines. Diamond appeals, therefore, the district court's denial of JMOL on these issues. FPS cross-appeals the jury's determination that claim 24 of the '505 patent and claim 28 of the '494 patent are not invalid. Because Diamond no longer pursues any claims arising from the '444 or '373 patents, or claim 34 of the '494 patent, this court need not address those questions. This court has jurisdiction over the present appeal under 28 U.S.C. § 1295(a)(1) (2000).

II.

This court reviews claim construction without deference. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1454, 46 USPQ2d 1169, 1172 (Fed. Cir. 1998) ( *en banc*). This court accords substantial deference to a jury's factual application of a claim construction to the accused device in an infringement determination. *Embrex, Inc. v. Serv. Eng'g Corp.*, 216 F.3d 1343, 1348-49, 55 USPQ2d 1161, 1164 (Fed. Cir. 2000).

This court reviews a district court's denial of JMOL without deference, reversing only if substantial evidence does not support a jury's factual findings or if the law cannot support the legal conclusions underpinning the jury's factual findings. *Cybor Corp.*, 138 F.3d at 1454. "A district court may overturn a jury's verdict only if upon the record before the jury, reasonable jurors could not have reached that verdict." *LNP Eng'g Plastics, Inc. v. Miller Waste Mills, Inc.*, 275 F.3d 1347, 1353, 61 USPQ2d 1193, 1197 (Fed. Cir. 2001).

Claim language defines claim scope. *SRI Int'l v. Matsushita Elec. Corp.*, 775 F.2d 1107, 1121, 227 USPQ 577, 586 (Fed. Cir. 1985) ( *en banc*). As a general rule, claim language is given the ordinary meaning of the words in the normal usage of the field of the invention. *Toro Co. v. White Consol. Indus.*, 199 F.3d 1295, 1299, 53 USPQ2d 1065, 1067 (Fed. Cir. 1999). Nevertheless, the inventor may act as his own lexicographer and use the specification to supply new meanings for terms either explicitly or by implication. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979, 34 USPQ2d 1321, 1330 (Fed. Cir. 1995) ( *en banc*), *aff'd*, 517 U.S. 370, 38 USPQ2d 1461 (1996). Thus, to help determine the proper construction of a patent claim, a construing court consults the written description, and, if in evidence, the prosecution history. *Id.* at 979-80.

After claim construction, the fact finder compares the properly construed claim with the allegedly infringing devices. *Kemco Sales, Inc. v. Control Papers Co.*, 208 F.3d 1352, 1360, 54 USPQ2d 1308, 1312 (Fed. Cir. 2000). Infringement requires the patentee to show that the accused device contains or performs each limitation of the asserted claim, *Mas-Hamilton Group v. LaGard, Inc.*, 156 F.3d 1206, 1211, 48 USPQ2d 1010, 1014-15 (Fed.

Cir. 1998), or an equivalent of each limitation not satisfied literally, *Warner-Jenkinson Co. v. Hilton Davis Chemical Co.*, 520 U.S. 17 [ 41 USPQ2d 1865] (1997). The sale or manufacture of equipment to perform a claimed method is not direct infringement within the meaning of 35 U.S.C. § 271(a). *Mendenhall v. Cedarapids, Inc.*, 5 F.3d 1557, 1579, 28 USPQ2d 1081, 1100 (Fed. Cir. 1993).

In this case, the record shows that FPS's customers use the method of the Moba Omnia to process eggs in the United States. Hence, to show infringement Diamond needs only to prove that the Moba Omnia performs the method of claim 24 when it processes eggs.

"guiding steps"

] Based upon its claim construction, the district court instructed the jury, in relevant part, that the guiding steps of claim 24 "are defined as follows: (1) Carrying eggs to holding ***1434** stations; (2) Carrying eggs from the holding stations to the spaced apart location; and (3) Carrying more eggs to the holding stations." At trial, Diamond did not object to either the district court's construction of "guiding steps" or to the jury instructions about that term. Following the jury verdict of non-infringement, the district court denied Diamond's JMOL motion. In its denial, the district court acknowledged that its interpretation of guiding steps left undetermined whether the claim requires sequential performance of the steps. Then the trial court reasoned that the jury reasonably could have determined from the testimony presented that sequential performance is a necessary characteristic of the "guiding steps." The district court's instructions to the jury did not require sequential performance. In essence, the district court allowed the jury to add an additional limitation to the district court's construction of "guiding steps." In this, the district court erred. Claim construction is a question of law and is not the province of the jury. *Markman*, 52 F.3d at 979.

This error takes on significance in this appeal because the jury found that the Moba Omnia does not infringe. The record before us discloses no alternative basis upon which a reasonable jury could find that the Moba Omnia does not infringe, other than that the Moba Omnia does not satisfy the guiding steps limitation. Thus, by allowing the jury to import an additional limitation into the claims, the district court fundamentally altered the verdict.

Because Diamond did not object to the district court's claim construction or instructions to the jury, FPS contends that Diamond has waived its right to argue the interpretation of "guiding steps" on appeal. The doctrine of waiver as applied to claim construction prevents a party from offering a new claim construction on appeal. *Interactive Gift Express v. Compuserve Inc.*, 256 F.3d 1323, 1346, 59 USPQ2d 1401, 1418 (Fed. Cir. 2001). Moreover, a party's objection to a jury instruction is waived unless that party objects to the instruction before the jury retires to consider the verdict. Fed. R. Civ. P. 51. In this case, however, waiver does not bar Diamond's argument. Diamond does not now contest the district court's instruction to the jury on the meaning of "guiding steps." Essentially Diamond does not wish to alter the district court's claim construction on appeal, but seeks enforcement of the trial court's claim construction.

Diamond has argued consistently, in its JMOL motions and in its argument on appeal here, that "[n]either the language of the claim itself nor the Court's order defining this language requires that the 'guiding steps' occur separately." Thus, Diamond has consistently protested the error that this court currently reviews on appeal. Thus, this court will not apply waiver to prevent Diamond from protecting the original breadth of the binding claim construction presented by the district court to the jury from *post facto* imposition of an additional limitation. *Interactive Gift Express*, 256 F.3d at 1346. Application of waiver in this case would essentially render unreviewable the district court's error. In sum, Diamond has not waived its argument that the guiding steps may be performed simultaneously.

Nowhere does the plain language of claim 24 require separate and consecutive performance of the various guiding steps. Rather, such a construction is contrary to the teachings of the '505 patent. For example, the specification explicitly describes simultaneous performance of guiding steps two and three. '505 patent, col. 5, l. 54 to col. 6, l. 3. Moreover, simultaneous performance of the guiding steps is consistent with operating at a significant

rate of speed, a stated object of the invention. '505 patent, col. 2, ll. 3- 7. The prosecution history is also consistent with this claim construction. Hence, this court, like the district court as well, construes the guiding steps to include simultaneous performance.

] FPS argues that, irrespective of whether claim 24 allows simultaneity, the method practiced by the Moba Omnia cannot infringe literally because it does not perform entirely at least one of the required guiding steps. This argument simply repackages FPS's argument for sequential performance of the guiding steps. FPS's argument focuses on distinctions between the Moba Omnia and the patentee's preferred embodiment for the claim 24 method. This court has discredited an infringement analysis for method claims that examines distinctions between implementing apparatuses. *Amstar Corp. v. Envirotech Corp.*, 730 F.2d 1476, 1482, 221 USPQ 649, 653 (Fed. Cir. 1984) ("[T]he law recognizes the irrelevance of apparatus distinctions in determining infringement of process claims.").

Like the device of Fig. 2, the Moba Omnia lifts eggs to an overhead conveyor for transport. To position the eggs for lifting, the Moba Omnia employs a continuously moving transport conveyor that slows without stopping as each egg passes under the overhead conveyor. ***1435** In these actions, the Moba Omnia practices all three guiding steps. With a focus on the movement of the eggs (the subject matter of the method claim) in the Moba Omnia, rather than the movement of the Moba Omnia itself, each of these steps is evident. As required by the first guiding step of claim 24, the Moba Omnia moves a first egg to a holding station. The Moba Omnia then moves the first egg to a spaced-apart location, the second guiding step. Simultaneously, the Moba Omnia moves a second egg to the holding station to perform the third guiding step. The first and second eggs are then ready for simultaneous lifting. In sum, the record evidence provides no basis upon which a reasonable jury could find that the Moba Omnia does not perform the three guiding steps of the '505 patent's claim 24.

"holding station"

] The district court correctly construed the "holding station" of claim 24 of the '505 patent as "a first location in space to which an egg is moved and at which the egg may maintain position until the egg is lifted simultaneously with an egg at a 'spaced-apart location.'" Nonetheless, FPS argues that the district court's construction requires that an egg cease motion before the lift to the overhead conveyor. The claims simply do not require a specific temporal limitation associated with the term "holding." Indeed the specification states that the holding station positions an egg relative to the overhead conveyor for pick-up to the overhead conveyor. *See, e.g.*, '505 patent, col. 2, ll. 44-58, col. 6, ll. 4-8. The specification actually speaks of eggs that are "held" as they move. *Id.* at col. 5, ll. 2-6 ("The disks each include a plurality of peripheral recesses which are disposed in horizontal alignment so as to receive and hold eggs advanced along the guide bars as they are transferred to the holding stations."). Moreover, the ordinary meaning of "to hold" is "to keep in position, guide, control, or manage." *The Oxford English Dictionary* (2d ed. 1989). This meaning also imposes no requirement that an object remain stationary.

Moreover, as this court has repeatedly counseled, the best indicator of claim meaning is its usage in context as understood by one of skill in the art at the time of invention. *Markman*, 52 F.3d at 986. In this instance, the context is the swift and safe movement of eggs. As indicated by the specification, the process holds the egg at the same time it moves the egg, thus achieving the dual goals of precision and speed. The process may hold and move an egg at the same time. In sum, the district court correctly construed the term "holding." The term "holding station" also does not require lack of motion.

To show that the Moba Omnia does not include a holding station, FPS relies entirely upon evidence that eggs in the Moba Omnia do not stop before they are picked up. As described above, however, the claim does not require a stationary holding station. To satisfy the holding station requirement, the Moba Omnia needs only employ "a first location in space to which an egg is moved and at which the egg may maintain position until the egg is lifted simultaneously with an egg at a 'spaced-apart location,'" whether or not eggs stop before the pick up. The record shows that the Moba Omnia

employs such a first location. In view of the undisputed record evidence, no reasonable jury could find that the Moba Omnia does not move an egg to a holding station as claimed.

In sum, the evidence of record consistent with the correct claim construction shows that the method performed by the Moba Omnia includes all three "guiding steps" and that the Omnia moves eggs to a "holding station." Because no reasonable jury could find on the record evidence that the method performed by the Moba Omnia does not infringe literally and directly claim 24 of the '505 patent, the district court erred in not granting JMOL on that issue.

B.

Turning to claim 28 of the '494 patent, the parties dispute the district court's construction of the limitation "predetermined sequence" and two limitations containing the phrase "downwardly and away." Because construction of the first "downwardly and away" limitation disposes of the question of infringement, this court need not address the other limitations.

The first "downwardly and away" limitation recites: " *rotating the receiving means downwardly and away from said first conveyor means to urge the received eggs downwardly*." The district court construed this claim language: "[T]he receiving means must be rotated downwardly (i.e. toward the ground) and be rotated away from the main ***1436** egg-carrying conveyor from which the eggs are released." With some slight clarification, the district court construed this claim limitation correctly. The slight clarification notes that the limitation constrains the motion of the received eggs as well as the motion of the receiving means. Specifically, the first "downwardly and away" limitation also requires that the receiving means move the eggs downwardly.

The claim recites that the receiving means "urge[s] the received eggs downwardly." The patent does not explicitly define "urge." In one sense, "to urge" means simply to press or to push. *See, e.g., The Oxford English Dictionary* (2d ed. 1989). This meaning of "urge," however, would place the preferred embodiment outside the claim scope. *Vitronics*, at 1583 (a claim interpretation that puts the preferred embodiment outside the claim is "rarely, if ever, correct and would require a highly persuasive evidentiary support."). Moreover this definition of "urge" makes infringement depend on the downward force exerted on the eggs by the rotating receiving means. A receiving means, such as that shown in Fig. 4 of the '494 patent, may rotate downward slowly and support the received eggs against the force of gravity. In doing so, the downward rotation would exert an upward force on the received eggs, i.e., it would "urge" the received eggs upward rather than downward as claim 28 requires. The patent does not show, however, that the downward force is a defining limitation.

] Another ordinary meaning of "to urge" avoids exclusion of the preferred embodiment from the claims. Specifically, "to urge" may mean "[t]o cause to move, hasten, or gather speed." *The Oxford English Dictionary* (2d ed. 1989). This definition receives support from the patent specification. The specification clarifies that "to urge" means broadly to move or to carry and that the receiving means may slow the motion of the eggs. For example, the patent specification notes that the receiving means " *reduce[s]* the speed at which the eggs fall and *gently move[s]* the eggs downwardly and outwardly away from carriage assemblies." '494 patent, col. 5, ll. 55-57 (emphases added); *see also Id.* col. 6, ll. 64-64, col. 7, ll. 1-3. Thus, in the context of this patent, this court employs the broader meaning of "to urge," namely, to cause to move.

The Staalkat Selecta employs a brush belt to receive eggs, as shown below. Once the brush belt receives the eggs, it transports the eggs horizontally to a comb mechanism that lifts the eggs from within the bristles of the brush belt. The comb then guides the eggs downward to a second transport conveyor.

At trial, FPS presented substantial evidence that the brush belt of the Staalkat Selecta does not move the eggs downwardly as required by the literal language of claim 28. FPS also presented substantial evidence to support that the Staalkat Selecta does not infringe claim 28 under the doctrine of equivalents. For example, Dr. Kirk, an expert witness for FPS, testified that the Selecta's brush belt does not guide eggs downwardly. Rather, the brush guides eggs over a linear path rather than a curved path. As a result, the eggs moved upward

rather than downward relative to their initial position upon receipt in the brush belt. This evidence supports the jury's verdict of no infringement. Even applying the doctrine of equivalents, the Staalkat Selecta performs a different function in a different way to obtain a different result from the language of the claim limitation. Thus, substantial evidence supports the jury's finding that the Staalkat Selecta's method does not satisfy the first "downwardly and away" limitation of claim 28, either literally or under the doctrine of equivalents. Hence, this court affirms the district court's denial of JMOL. Because the Staalkat Selecta does not satisfy the first "downwardly and away" limitation, this court need not reach other potential grounds to support the jury's verdict.

III.

The Patent Act imposes indirect infringement liability on a party who actively induces others to directly infringe a patent. 35 U.S.C. § 271(b) (1994). Diamond appeals the district court's denial of its motion for JMOL that FPS indirectly infringes claim 24 of the '505 patent and claim 28 of the '494 patent. In reviewing ***1437** the district court's denial of Diamond's JMOL motion, this court presumes that the jury resolved all factual disputes in favor of the prevailing party and leaves those findings undisturbed as long as substantial evidence supports them. *Sibia Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1354, 55 USPQ2d 1927, 1930 (Fed. Cir. 2000).

The district court denied Diamond's JMOL on inducement because the jury determined that "none of the machines sold by FPS infringe any of the patents in suit." *Moba*, No. 95-CV-2631, 2000 U.S. Dist. LEXIS 15483, at *43. Because this court upholds the verdict that claim 28 of the '494 patent is not directly infringed, the trial court correctly determined that FPS does not indirectly infringe that claim. *Met-Coil Sys. Corp. v. Korners Unlimited, Inc.*, 803 F.2d 684, 687, 231 USPQ 474, 477 (Fed. Cir. 1986) ("[T]here can be no inducement of infringement without direct infringement by some party."). However, this court has held that the Moba Omnia method directly infringed claim 24 of the '505 patent. Therefore, the issue of infringement by FPS depends on whether FPS "actively induce[d] infringement" within the meaning of 35 U.S.C. § 271(b).

Although § 271(b) does not use the word "knowingly," this court has uniformly imposed a knowledge requirement. *Water Tech. Corp. v. Calco, Ltd.*, 850 F.2d 660, 7 USPQ2d 1097 (Fed. Cir. 1988); *C.R. Bard, Inc. v. Advanced Card. Sys., Inc.* 911 F.2d 670, 15 USPQ2d 1540 (Fed. Cir. 1990). This court defined the generally applicable intent standard in *Hewlett-Packard Co. v. Bausch & Lomb, Inc.*, 909 F.2d 1464, 1468-69, 15 USPQ2d 1525, 1528-29 (Fed. Cir. 1990). In *Hewlett-Packard* , this court held that "proof of actual intent to cause the acts which constitute the infringement is a necessary prerequisite to finding active inducement" under § 271(b). *Hewlett-Packard*, 909 F.2d at 1469. Hewlett-Packard Co. (HP), was the assignee of the LaBarre patent on aspects of X-Y plotter technology. Bausch & Lomb, Inc. (B & L), manufactured and sold X-Y plotters and a variety of other electronic equipment through a division that it sold to Ametek, Inc. HP alleged that B & L induced infringement of the LaBarre patent by its sale to Ametek. This court found, however, that the sale did not evince an intent to induce infringement but, rather, merely an intent to sell at the highest price. This court particularly noted that B & L had no interest in, nor control over, Ametek's use of the purchased division. Implicit in this court's determination was that Ametek could have employed the purchased division in a wide range of non-infringing activity. Moreover, this court noted that the agreement to develop a non- infringing plotter established, if anything, B & L's intent to avoid any inducement of infringement.

In this case, the only intent required of FPS is the intent to cause the acts that constitute infringement. *Hewlett-Packard*, 909 F.2d at 1469. Although Diamond argues that the record shows that FPS sold its customers the Moba Omnia and trained them to use the infringing method, active inducement is nonetheless a factual inquiry. Accordingly, this court declines to make a determination that no reasonable jury could conclude that FPS did not intend that its customers perform acts that constitute infringement. Therefore, this court remands for further inquiry into whether FPS indirectly infringes claim 24 of the '505 patent.

IV.

The Patent Act erects a presumption of validity for an issued patent. 35 U.S.C. § 282 (1994). Therefore, invalidity requires clear and convincing evidence. *Id.*; *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 54 USPQ2d 1673 (Fed. Cir. 2000). Because this court has determined that FPS may infringe claim 24 of the '505 patent, depending on resolution of the inducement issue, this court also addresses FPS's appeal of the jury verdict upholding the validity of that claim. FPS argues that the claim is invalid as anticipated, not enabled, and not adequately described.

A.

A patent specification must contain an adequate written description. 35 U.S.C. § 112, ¶ 1 (1994). Whether a specification complies with the written description requirement of § 112, ¶ 1 is a question of fact that this court reviews for substantial evidence. *Advanced Display Sys.*, 212 F.3d at 1281.

FPS argues here that if claim 24 of the '505 patent encompasses lifting eggs from a moving conveyor, as this court has determined, then claim 24 must be invalid because the '505 patent specification discloses no such conveyor mechanism. In support of this proposition, FPS cites to this court's decision in *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 45 USPQ2d 1498 (Fed. Cir. 1998).

Federal Circuit case law reflects two applications of 35 U.S.C. § 112, ¶ 1. First, in 1967, ***1438** this court's predecessor inaugurated use of § 112 to prevent the addition of new matter to claims. *In re Ruschig*, 379 F.2d 990, 154 USPQ 118 (CCPA 1967). As this court's predecessor noted, "[t]he function of the description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him." *In re Wertheim* , 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). Although the statute proscribes addition of new matter to a specification or claims under § 132, the United States Court of Customs and Patent Appeals decided to police the addition of new matter to claims separately using § 112. *In re Rasmussen*, 650 F.2d 1212, 1214, 211 USPQ 323, 325-26 (CCPA 1981). This court's predecessor explained that the use of § 132 or § 112 was synonymous because "a rejection of an amended claim under § 132 is equivalent to a rejection under § 112, first paragraph." *Id.* Since then, this court has continued to use § 112 to ensure that a patentee had possession at the time of filing of subject matter subsequently claimed. In this court's most recent application of the written description doctrine, it noted: "The purpose of the written description requirement is to prevent an applicant from *later* asserting that he invented that which he did not; the applicant for a patent is therefore required 'to recount his invention in such detail that his *future* claims can be determined to be encompassed within his *original*, creation.'" *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 314 F.3d 1313, 1330, 65 USPQ2d 1385, 1397 (Fed. Cir. 2003) (citing *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991)). In that setting, the written description is the metric against which a subsequently added claim is measured to determine if it is due the priority date of the original patent. *Id.* at 1560 ("The question raised by these situations is most often phrased as whether the application provides 'adequate support' for the claim(s) at issue; it has also been analyzed in terms of 'new matter' under 35 U.S.C. § 132."); *In re Wright*, 866 F.2d 422, 424, 9 USPQ2d 1649, 1651 (Fed. Cir. 1989) ("When the scope of a claim has been changed by amendment in such a way as to justify an assertion that it is directed to a different invention than was the original claim, it is proper to inquire whether the newly claimed subject matter was described in the patent application when filed as the invention of the applicant. That is the essence of the so-called 'description requirement' of § 112, first paragraph.").

In *Gentry Gallery*, the patentee described in the specification a sectional sofa with a center console including recliner controls. The specification as filed clearly identified the console as the only possible location for the controls. From the specification, it was clear that the patentee considered placement of the controls in the center console "to be an essential element of his invention." *Gentry Gallery*, 134 F.3d at 1479. Hence, this court limited the scope of the patentee's claims to a sofa with controls located in a center console: "Accordingly, [the patentee's] original disclosure serves to limit the permissible breadth of his *later-drafted claims*." Id. at 147 (emphasis

added). Thus, because *Gentry Gallery* applied § 112 , ¶ 1, to hold the patentee to the scope of its original filing, it does not apply in this case where FPS made no allegation at all that the disclosure of the '505 patent did not show possession of a later-filed claim.

The second application of the written description requirement is reflected in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). There, this court invoked the written description requirement in a case without priority issues. Invoking § 112, *Lilly* required a precise definition of a DNA sequence in the patent specification. In more recent cases, however, this court has distinguished *Lilly*. For instance, in *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002), neither the specification nor the deposited biological material recited the precise "structure, formula, chemical name, or physical properties" required by *Lilly*. *Id.* at 1324 (quoting *Lilly*, 119 F.3d at 1566). Although this court initially determined that the specification in *Enzo* did not satisfy the *Lilly* disclosure rule, it revisited the issue and remanded to the district court. The court instructed:

On remand the court should determine whether a person of skill in the art would glean from the written description, including information obtainable from the deposits of the claimed sequences, subsequences, mutated variants and mixtures sufficient to demonstrate possession of the generic scope of the claims.

*Enzo*, 296 F.3d at 1328. Similarly, in this court's most recent pronouncement, it noted:

More recently, in *Enzo Biochem*, we clarified that *Eli Lilly* did not hold that all functional ***1439** descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure. *Amgen*, 314 F.3d at 1332.

] The test for compliance with § 112 has always required sufficient information in the original disclosure to show that the inventor possessed the invention at the time of the original filing. *See Vas-Cath*, 935 F.2d at 1561 ("Adequate description of the invention guards against the inventor's overreaching by insisting that he recount his invention in such detail that his future claims can be determined to be encompassed within his original creation"). The possession test requires assessment from the viewpoint of one of skill in the art. *Id.* at 1563-64 ("the applicant must . . . convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*") (emphasis in original); *Union Oil Co. of Cal. v. Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 USPQ2d 1227, 1232 (Fed. Cir. 2000) ("The written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed'") (citation omitted). In *Enzo* and *Amgen*, the record showed that the specification that taught one of skill in the art to make and use an invention also convinced that artisan that the inventor possessed the invention. Similarly in this case, the *Lilly* disclosure rule does not require a particular form of disclosure because one of skill could determine from the specification that the inventor possessed the invention at the time of filing.

Accordingly, substantial evidence supports the jury's finding that the '505 patent is not invalid for lack of an adequate written description. The '505 patent specification describes every element of claim 24 in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the invention at the time of filing. FPS's contention that the '505 patent does not adequately disclose lifting eggs from a moving conveyor merely revives its non-infringement argument in the cloak of a validity challenge. As noted, the jury found that one of skill in the art would discern possession of the invention at the time of filing, a finding supported by substantial record evidence. Therefore, the trial court correctly determined that claim 24 is not invalid for lack of an adequate written description.

B.

The patent specification must disclose information

sufficient to enable those skilled in the art to make and use the claimed invention. 35 U.S.C. § 112 ¶ 1 . That some experimentation is required to practice the claimed invention is permissible, so long as it is not undue. *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). Enablement under 35 U.S.C. § 112, ¶ 1, is a question of law that this court reviews *de novo*. *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1268, 229 USPQ 805, 810 (Fed. Cir. 1986). This court reviews a jury's underlying factual determinations related to enablement for substantial evidence. *Mitsubishi Elec. Corp. v. Ampex Corp.*, 190 F.3d 1300, 1309, 51 USPQ2d 1910, 1916 (Fed. Cir. 1999).

] FPS contends that the specification does not enable one of ordinary skill in the art to lift eggs from a moving conveyor belt without undue experimentation. Nevertheless, FPS presented no record evidence recounting the amount of experimentation one of skill in the art would require to develop the conveyor lifting system of the Moba Omnia in view of the '505 patent disclosure. Rather, FPS asked the jury and asks this court to draw the inference of undue experimentation based on limited general testimony of the development of that conveyor lifting mechanism taken separate from the disclosure of the '505 patent. The trial court found that evidence insufficient to prove undue experimentation. Hence, this court holds that substantial evidence supports the verdict of the jury that claim 24 was not invalid for lack of enablement.

C.

Anticipation under 35 U.S.C. § 102 requires that a single prior art reference disclose each and every limitation of the claimed invention. *Electro Med. Sys. S.A. v. Cooper Life Sci.*, 34 F.3d 1048, 1052, 32 USPQ2d 1017, 1019 (Fed. Cir. 1994). This court reviews a jury's conclusions on anticipation for substantial evidence. *Advanced Display Sys.*, 212 F.3d at 1281.

FPS argues that claim 24 of the '505 patent is anticipated by its own Moba prior art machines, such as the Types 4-9 or Type 68 machines that provided the basis for the Omnia ***1440** lifting mechanism. Nevertheless, as was testified by FPS's own expert witness, Dr. Kirk, those prior art Moba machines do not continuously advance eggs through weighing stations while simultaneously weighing the eggs, as is required by claim 24. Hence, this court finds that claim 24 is not anticipated as a matter of law by the asserted Moba prior art machines.

In sum, because substantial evidence supports the jury verdict that claim 24 of the '505 patent is not invalid, this court affirms that portion of the district court judgment.

CONCLUSION

The district court correctly determined that substantial evidence supports the jury verdict that FPS does not infringe claim 28 of the '494 patent. This court affirms, therefore, the district court's denial of Diamond's JMOL motion on that issue. Because FPS does not infringe the '494 patent, this court makes no determination as to that patent's validity. On claim 24 of the '505 patent, this court remands for further determination of whether FPS induced its customers to infringe under a correct reading of that claim. This court reverses, therefore, the district court's denial of JMOL on those issues and remands. Because substantial evidence supports the validity of properly construed claim 24, this court affirms that portion of the district court's judgment.

COSTS

Each party shall bear its own costs.

AFFIRMED-IN-PART, REVERSED-IN-PART, and REMANDED

FN3. The district court determined that the language "receiving means" does not invoke § 112, ¶ 6. As the district court's failure to construe this limitation as means-plus-function is not disputed by the parties, this court offers no judgment on the correctness of that determination.

Rader, J., concurring.

This case reveals a distinct institutional difference between the United States Court of Appeals for the Federal Circuit and the other twelve circuits. Whenever a Federal Circuit panel makes an error interpreting the patent code, every district court in the nation, and even every later Federal Circuit panel, is obliged to follow and perpetuate the error. Even the Supreme Court has difficulty identifying errors for correction because this court's national jurisdiction requires universal application of a mistake. This particular *Moba* case does not originate, but perpetuates such an error.

This mistake misapplies both the statutory law and the policy underlying United States patent law. Specifically; this court - contrary to the statute and its own thirty-year body of case law - applies the written description doctrine beyond the purpose for which the doctrine was created, namely priority protection. By making written description a free-standing disclosure doctrine, this court produces numerous unintended and deleterious consequences.

I.

This case illustrates some of the unintended consequences of this judge-made doctrine. Each time a claim encompasses more than the preferred embodiment of the invention described in the specification, a defendant can assert that the patent is invalid for failure to describe the entire invention. Under the expanded written description doctrine, every claim construction argument could conceivably give rise to a validity challenge as well. In this case, for instance, FPS Food Processing Systems, Inc. ("FPS") argues if claim 24 of the '505 patent encompasses lifting eggs from a moving conveyor, as this court has determined, then claim 24 must be invalid because the '505 patent specification discloses no such conveyor mechanism. FPS's routine claim construction argument becomes a validity challenge under the non-statutory doctrine created in the *Lilly* case. *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Fortunately, this court did not fall for FPS's argument.

Unfortunately, however, this court is not the only judicial actor that must deal with the unintended consequences of the *Lilly* doctrine. Because FPS argued that the specification did not disclose some feature of the claimed invention, the trial court had to take extensive testimony and ask a jury to speculate whether one of skill in the art would have known that the inventor "possessed" the full invention.

The trial court faced even greater confusion because FPS also asserted that the specification does not enable the claimed invention. Thus, the trial court asked this jury to determine whether one of skill in the art would have been able to make and use the invention based on the patent's specification. Then the trial court asked to jury to look at the specification again to determine whether the inventor "possessed" the invention. Thus, this jury faced the cumbersome task of separating two doctrines for sufficiency of disclosure in a patent. Under Federal Circuit case law, FPS asked this jury to decide that the patent's disclosure can enable a skilled artisan to make and practice the entire invention, but still not inform that same artisan that the inventor was ***1441** in possession of the invention. Puzzling. Moreover, the trial court had to give separate instructions and entertain separate witnesses on these inseparable patent rules to ensure full disclosure. The *Lilly* doctrine simply makes no sense in this context. In fact, outside its proper context of policing priority, it never makes sense but compounds the confusion, increases the chances for error, and augments the expense of the trial process.

II.

The Patent Act refers to "a written description" in 35 U.S.C. § 112, ¶ 1:

*The specification shall contain a written description of the invention*, and of the manner and process of making and using it, in such full, clear, concise, and exact terms *as to enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the same*, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

35 U.S.C. § 112, ¶ 1 (2000) (emphasis added). The language of § 112, ¶ 1 indicates that a patent

will contain an adequate description if it provides enough information to enable a person skilled in the art to make and use the invention. Any disclosure that enables one to make and use the invention also, by definition, also shows that the inventor was in possession of that full invention. Consequently, the erroneous written description requirement of *Lilly* case lacks both a statutory and a logical foundation.

This origins of the *Lilly* error have been explored at length in *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 63 USPQ2d 1609, 1628 (app.) (Fed. Cir. 2002) (rehearing en banc denied) (Rader, J., dissenting). Before 1967, written description was not a requirement separate from enablement. In *In re Ruschig*, this court's predecessor court created a new written description requirement for the sole purpose of enforcing priority issues. *See In re Ruschig*, 379 F.2d 990, 154 USPQ 118 (CCPA 1967). The court in *Ruschig* used § 112, ¶ 1 to reject later-drafted claims that encompassed subject matter not disclosed by the original claims and specification. A section of title 35, specifically § 132 , directly prohibits the addition of new matter to a disclosure, either in the claims or the rest of the patent application. Nonetheless, this court's predecessor decided to use § 112 to prevent the addition of new matter to claims, rather than the specific provisions of § 132. This extra license with the language of title 35 did no harm because the Court of Customs and Patent Appeals recognized "that a rejection of an amended claim under § 132 is equivalent to a rejection under § 112, first paragraph." *In re Rasmussen*, 650 F.2d 1212, 1214, 211 USPQ 323, 325 (CCPA 1981).

Thus, from 1967 until 1997, the new matter doctrine, cloaked either in the specific language of § 132 or the innovative new reading of § 112, operated only to determine whether new claim language deserved priority back to the patent's original filing date. In other words,

[w]hen the scope of a claim has been changed by amendment in such a way as to justify an assertion that it is directed to a different invention than was the original claim, it is proper to inquire whether the newly claimed subject matter was described in the patent application when filed as the invention of the patents. *That is the essence of the so-called 'description requirement' of § 112, first paragraph.*

*In re Wright*, 866 F.2d 422, 424, 9 USPQ2d 1649, 1651 (Fed. Cir. 1989) (emphasis added).

The new matter doctrines did not extend beyond priority issues because § 112 already supplies enablement to ensure that an inventor adequately describes the invention in exchange for temporary rights of exclusivity. For over thirty years, this court and its predecessor understood this basic principle of patent law and confined the written description doctrine to its purpose - policing priority of invention. [FN1]

In 1997, this court inexplicably wrote a new disclosure requirement, found nowhere in title 35, and attributed that new requirement to the written description doctrine. This new disclosure doctrine, applied so far only to biotechnology cases, requires a nucleotide-by-nucleotide recitation of the structure of a biotechnological invention. *Lilly*, 119 F.3d at 1567. Ironically, this court could have reached the same result in *Lilly* without making a new disclosure rule. Under the statute's enablement rule, this court would have also determined that the invention was not sufficiently ***1442** disclosed. [FN2] Instead, this court presumed to create another doctrine for sufficiency of disclosure. Although characterized as a written description doctrine, the *Lilly* rule cannot in fact trace its origin to the statute or to any prior case. *See generally Enzo*, 63 USPQ2d at 1627-29.

Confusing the *Lilly* disclosure doctrine with the traditional written description doctrine, this court has stated that written description is separate from enablement. *See Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 65 USPQ2d 1385 (Fed. Cir. 2003). Of course, this proposition is true with respect to the traditional written description/new matter doctrine. On the other hand, the only way to distinguish the *Lilly* rule from enablement is to construe *Lilly* as requiring more disclosure than necessary to enable one of skill in the art to make and use the invention, a "super-enablement" standard. [FN3] Interpreting *Lilly* in those terms, however, presents severe consequences for biotechnology. For biotechnological inventions, *Lilly* purports to require the recitation, nucleotide by nucleotide, of the entire sequence of a new protein or composition. This non- statutory rule jeopardizes the validity of many inventions in biotechnology patented from the advent of the

biotech era in the late 1970s. Before judicial creation of the *Lilly* rule in 1997, no inventor could have foreseen that the Federal Circuit would make a super-enablement rule. Without any way to redraft issued patents to accommodate the new rule, a large number of patents in the field of biotechnology face serious and unavoidable validity challenges.

Even if a drafter of biotechnological patents now knows the new law, compliance may tax a drafter beyond reasonable limits. A new protein or other DNA-related discovery may contain a chain of hundreds of amino acids. Many of the amino acids in the chain have substitutes that may take their place without altering the functional properties of the protein. Consequently, a "precise definition" [FN4] of the new protein, as required by *Lilly*, apparently requires tedious disclosure of thousands of potential permutations of the amino acid sequence that all fall within a proper description of the protein's functions, properties, and DNA source.

This burdensome disclosure standard is tantamount to requiring disclosure, for a new software invention, of the entire source code, symbol by symbol, including all source code permutations that would not alter the function of the software. Ironically, the Federal Circuit has expressly rejected such a requirement for software inventions, but apparently enforces the requirement for biotechnology. *See e.g. N. Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 15 USPQ2d 1321 (Fed. Cir. 1990) (overturning a finding that a patent did not adequately disclose "batching" software). This discrepancy emphasizes another problematic aspect of the *Lilly* doctrine. That is, it imposes a different disclosure standard for biotechnology than for computer technology. Despite the technology-neutral language of the Patent Act, the *Lilly* rule imposes technology-specific requirements.

Returning to the consequences of the *Lilly* rule for biotechnology, the burdens of this elevated "precise definition" standard unnecessarily increase the cost and time required to prepare and prosecute a biotechnology patent. Moreover, university inventors and non-corporate biotechnologists must endure significant expense and delay to acquire the sequence of a potential invention for disclosure under the *Lilly* rule. Sequencing is very expensive. ***1443** Consequently, the *Lilly* rule can also have the unintended consequence of pricing non-corporate inventors out of the inventive market for biotechnology.

III.

Fortunately, the viability of the *Lilly* rule is on the decline. After *Enzo*, this court recognized "that *Ely Lilly* did not hold that all functional descriptions of genetic material necessarily fails as a matter of law to meet the written description requirement, rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." *Amgen*, 314 F.3d at 1332, 1361 (dissent: "[T]he majority . . . verges on confining *Ely Lilly* to its facts.").

In this case, as in *Enzo*, the court explained that the written description requirement is satisfied when "one of skill in the art would discern possession of the invention at the time of filing." Indeed, the *Enzo* court struggled to distinguish the so-called written description requirement from enablement. In reversing its original decision that deposits of biological material do not satisfy the written description requirement, the *Enzo* panel cited cases that found that such deposits satisfy the enablement requirement. [FN5] In other words, because *Lilly* did in fact compel the result of the original *Enzo* panel, the court on reconsideration had to concede that deposited material satisfies the *Lilly* standard if it meets the enablement standard.

With some understanding of the difficulties and redundancy of the *Lilly* rule, the Federal Circuit has begun to convert it into the enablement doctrine with a different label. Unfortunately that leaves trial courts in the fix that the trial court faced in this case - presenting the jury two disclosure doctrines with apparently overlapping requirements. After all, to enable is to show possession, and to show possession is to enable. [FN6]

IV.

In sum, the *Lilly* rule is not just a mere one-time mistake. It defies over thirty years of case law. It finds no specific support in any statutory language. It creates a technology-specific rule in a technology-neutral statute. It distorts the statute's rules for adequate disclosure of inventions. It

complicates biotechnology patent drafting to the point of near impossibility and invites invalidating mistakes. It prices non-corporate inventors out of some biotechnological invention markets. Last, but not least, it burdens both trial and appellate courts with unnecessary and confusing procedures in otherwise simple cases like this one.

Of course, this court should recognize and prevent, rather than ignore and create, mistakes in the interpretation of the Patent Act. In the rare event that this court makes this type of error, this Circuit has a unique obligation to swiftly pursue *en banc* correction. Unlike regional circuits, this court cannot rely on circuit splits to identify an issue for Supreme Court correction. Moreover this court's jurisdiction over patents requires every trial court and this court itself to multiply this type of error until corrected. Accordingly, this court has a greater responsibility to pursue *en banc* correction of serious errors in interpretations of the Patent Act, such as the *Lilly* rule.

Alternatively, as indicated in Judge Bryson's concurring opinion, the problem in this area of the law may lie in the line of cases stemming from the *Ruschig* case. In that context, I agree that all priority issues can be more than adequately resolved under the new matter doctrine in 35 U.S.C. § 132.

FN1. *See generally Enzo Biochem, Inc. v. Gen-Probe, Inc.*,63 USPQ2d 1609, 1628 (Fed. Cir. 2002) (app.) (rehearing en banc denied) (Rader, J., dissenting) (quoting from every written description case, except *Lilly*, to show they only employed the doctrine to police priority).

FN2. U.S. Patent No. 4,652,525, at issue in *Lilly*, claimed priority to a parent application filed in 1977. The art of biotechnology was in its early stages in 1977. Under a proper enablement analysis, the simple disclosure of human insulin cDNA in the '525 patent would have failed to enable a person skilled in the art in 1977 to practice the claimed invention. Thus, the claims at issue would have been found invalid for lack of enablement.

FN3. *See* Rai, Arti, "Intellectual Property Rights in Biotechnology: Addressing New Technology" 34 *Wake Forest L. Rev.* 827, 834-35 (Fall, 1999) ("the *Lilly* court used the written description requirement as a type of elevated enablement requirement."); Sampson, Margaret, "The Evolution of the Enablement and Written Description Requirements Under 35 U.S.C. § 112 in the Area of Biotechnology" 15 *Berkley Tech. L.J.* 1233, 1262 (Fall 2000) ("The primary argument against the Federal Circuit's heightened written description requirement for biotechnological invention is that . . . it also 'reduces incentives to invest in innovation by depriving potential patentees of the opportunity to fully benefit from their research.'"); Mueller, Janice M., "The Evolving Application of the Written Description Requirement to Biotechnological Inventions" 13 *Berkeley Tech. L.J.* 615, 617 (Spring 1998) ("The *Lilly* decision establishes uniquely rigorous rules for the description of biotechnological subject matter that significantly contort written description doctrine away from its historic origins and policy grounding. The *Lilly* court elevate[s] written description to an effective 'super enablement' standard . . ..").

FN4. *See Eli Lilly*, 119 F.3d at 1566 (citing the "precise definition" standard of *Fiers v. Revel*, 984 F.2d 1164, 1171 [25 USPQ2d 1601] (Fed. Cir. 1993)).

FN5. *See Enzo*, 296 F.3d at 1325 ("Whether reference to a deposit of a nucleotide sequence may adequately describe that sequence is an issue of first impression in this court. In light of the history of biological deposits for patent purposes [and] the goals of patent law . . . we hold that reference in the specification to a deposit in a public depository . . . constitutes an adequate description of the deposited material. . . . The practice of depositing biological material arose primarily to satisfy the enablement

requirement of § 112, ¶ 1") (citing *In re Argoudelis*, 434 F.2d 1390,168 USPQ 99, 100 (CCPA 1970) (finding that making the biological material accessible to the public enabled the public to make and use the claimed antibiotics)).

FN6. Patent scholars have encouraged this court to "resist the narcotic of the written description requirement and redirect [its] energies towards refining the enablement concept, particularly as it correlates to claim scope." Janis, Mark D., "On Courts Herding Cats: Contending with the 'Written Description' Requirement (and Other Unruly Patent Disclosure Doctrines)" 2 *Wash. U. J. L. & Pol'y* 55, 62, 107 (2000) ("the fault [for the confusion about the standard for patent disclosure] lies in the courts' hesitancy to explore the power of the enablement requirement.").

Bryson, J., concurring.

Having been a member of the panel that decided *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), I write to make a single point with regard to the court's decision in ***1444** that case. *Lilly* has been criticized as departing from prior law by applying the written description requirement for a purpose other than to police priority. Setting aside the question whether the disclosure requirement imposed in *Lilly* was unduly stringent, a point that Judge Rader addresses in his concurring opinion, I do not believe that *Lilly* constituted a departure from prior law when it applied the written description requirement in a non-priority context.

*In re Ruschig*, 379 F2d 990, 154 USPQ 118 (CCPA 1967), held that 35 U.S.C. § 112, paragraph 1, contains a written description requirement that is separate from the enablement requirement found in the same paragraph. That interpretation of the statute may or may not have been correct--there is something to be said for either side of that question of statutory construction. But there is no question that *Ruschig* and subsequent decisions have held that written description and enablement are separate statutory requirements, and that written description is not simply a facet of enablement. Judge Rader acknowledges as much, but argues that as long as the *Ruschig* doctrine was confined to cases involving priority disputes, that reading of the statutory language worked no particular mischief, as it was simply redundant of the statutory prohibition against new matter in 35 U.S.C. § 132. The problem, as I see it, is that if it is correct to read section 112 as containing a separate written description requirement, it is difficult to find a principled basis for restricting that requirement to cases involving priority disputes. There is no language in section 112 that would support such a restriction, and I am unaware of any other basis for construing the statute in that fashion, unless we are simply to announce that the *Ruschig* cases will be tolerated, but must be limited to their facts. Put another way, if the *Ruschig* line of cases is sound as a matter of statutory construction, it is difficult to see why that construction does not apply equally in the *Lilly* non-priority context.

Perhaps the entire line of cases stemming from *Ruschig* is wrong, and perhaps we should at some point address that question en banc. I take no position on that issue at this juncture. I think it is worth pointing out, however, that the real question raised by Judge Rader's statutory analysis is not whether *Lilly* was an unwarranted departure from the *Ruschig* line of cases, but whether that entire line of cases is based on a fundamentally flawed construction of 35 U.S.C. § 112, paragraph 1.

C.A.Fed.

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